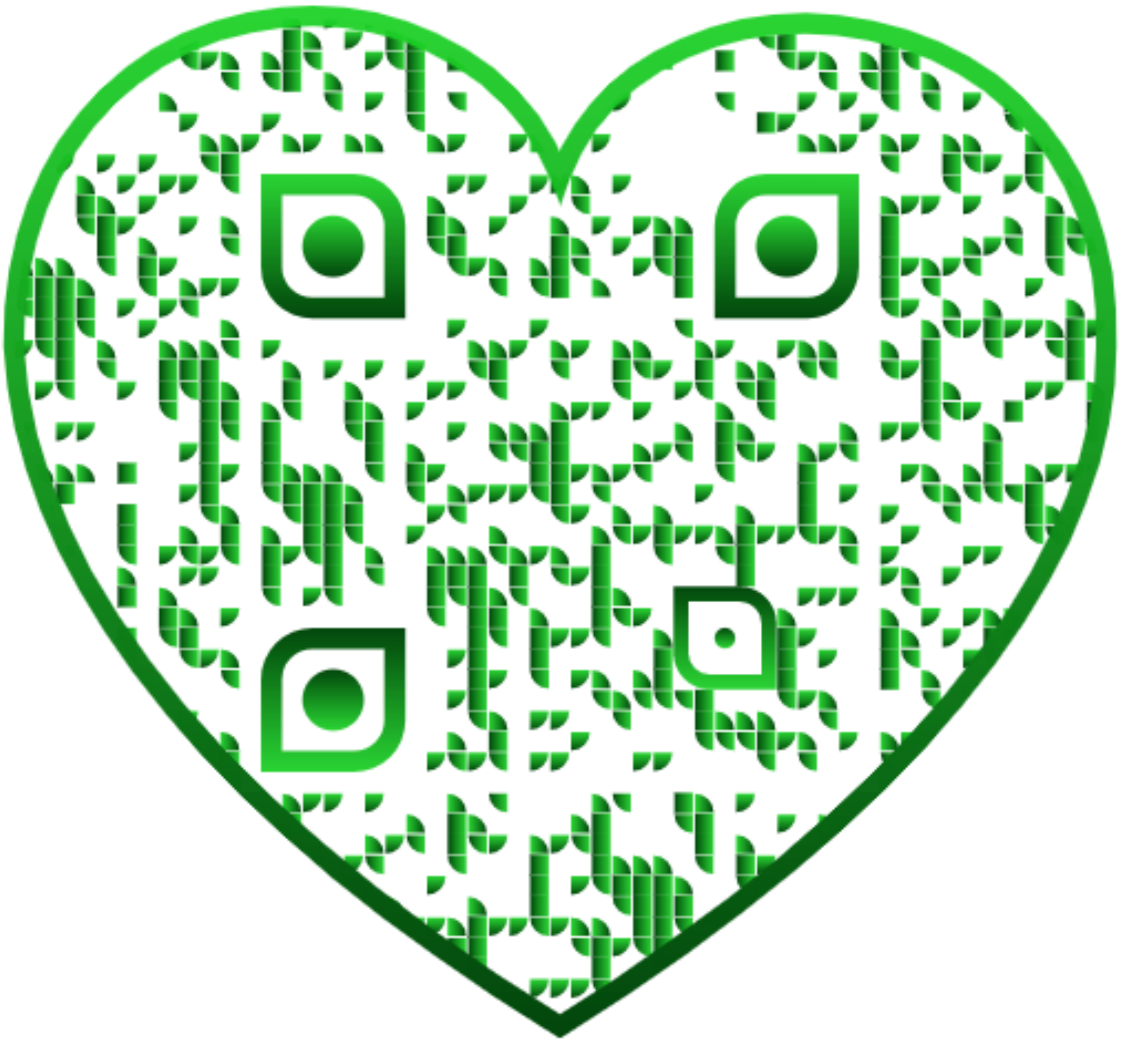
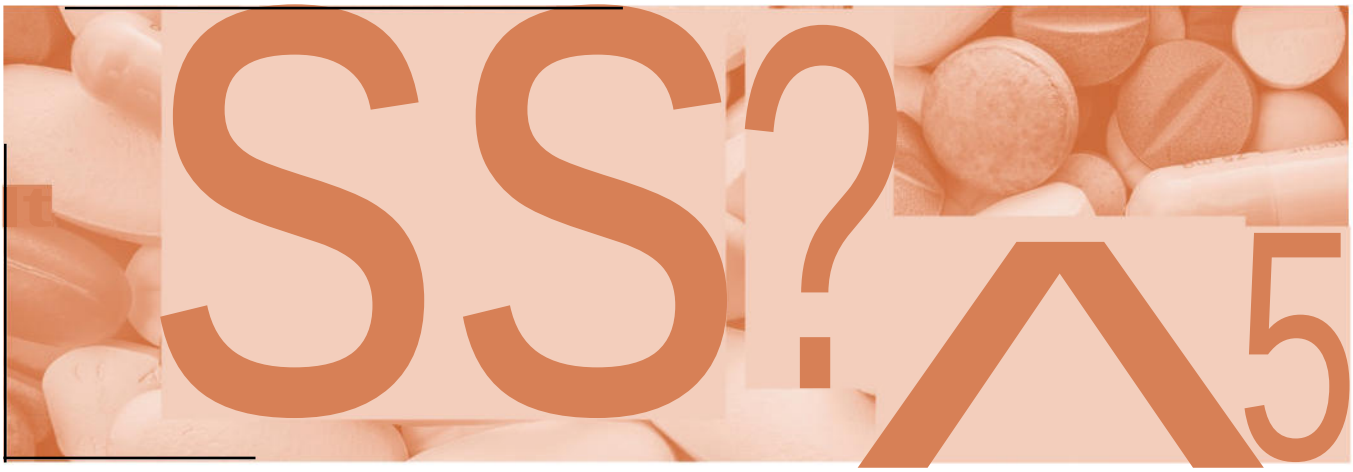
ANTIBIOTICS SIMPLIFIED

FIFTH EDITION

JASON C. GALLAGHER
CONAN MACDOUGALL





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Cover Images: Pills: © Eugen Wais/Envato ElementsBacteria: © Kateryna Kon/Shutterstock
Printing and Binding: McNaughton & Gunn

Library of Congress Cataloging-in-Publication Data
Library of Congress Cataloging-in-Publication Data unavailable at time of printing.
LCCN: 2021925089

6048

Printed in the United States of America
26 25 24 23 22 10 9 8 7 6 5 4 3 2 1

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ACKNOWLEDGMENTS

Our thanks go to those who helped edit all five editions of *Antibiotics Simplified* and to our wives, who put up with us and took care of our kids while we wrote the *Fifth Edition*.

We dedicate this text to the students of Temple University and the University of California, San Francisco. We hope you find it useful.

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INTRODUCTION

Antibiotics—the word sends terror coursing through the veins of students and makes many healthcare professionals uncomfortable. The category of antibiotics contains many different classes of drugs that differ in spectrum of activity, adverse effect profiles, pharmacokinetics and pharmacodynamics, and clinical utility. These classes can seem bewildering and beyond comprehension. We believe that taking a logical, stepwise approach to learning the pharmacotherapy of infectious diseases can help burn away the mental fog preventing optimal use and understanding of these drugs.

Learning the characteristics of antibiotics greatly simplifies learning infectious disease pharmacotherapy. Students and clinicians who attempt to learn the antibiotics of choice for different types of infections before knowing the characteristics of those drugs never truly understand the context of what they are attempting to learn, and those memorized facts usually don't stay in memory for long. Once the characteristics of the antibiotics are known, making a logical choice to treat an infection is much easier. This approach takes some time up front, but it will be well worth the effort when one realizes that the pharmacotherapy of *all* infections is fundamentally similar and logical. It also pays off when you encounter a patient who didn't read the guidelines for the infection they have and requires an antibiotic regimen outside the norm.

How to Use This Book

We wrote this book in an effort to condense the many facts that are taught about antibiotics in pharmacology and pharmacotherapy courses into one quick reference guide. It is meant to supplement material learned in pharmacology, not to supplant it. Use this book as a reference when you encounter a class of antibiotics that you know you have heard about; it will remind you of key points you may have forgotten.

This book contains six parts. Part 1 reviews basic microbiology and how to approach the pharmacotherapy of a patient with a presumed infection. The chapters in Parts 2–6 provide

concise reviews of various classes of antibacterial, antimycobacterial, antifungal, antiviral, and antiparasitic drugs, respectively. Again, this book is intended to supplement your other pharmacology textbooks. These chapters give key points about each class of antibiotics—they are not thorough reviews. The appendices contain references that may help in daily use.

Format of the Drug Class Reviews

Each drug class chapter follows the same basic format. The agents belonging to each class are listed first. Drugs available intravenously are *italicized*; those available orally are underlined.

Mechanism of Action

This section concisely summarizes the mechanism of action of the antibiotic class.

Spectrum

This section summarizes key organisms against which each class has or lacks activity. The spectra listed are not exhaustive.

Adverse Effects

This section lists key adverse effects. This list is not exhaustive, but it gives the most common and/or concerning adverse effects of each class.

Dosing Issues

This section discusses common problems or potential errors in drug dosing for select drug classes when they are present.

Important Facts

This section provides a summary of significant facts for and aspects of each drug class.

What They're Good For

This section lists some of the most common and/or useful indications for the agents in the class. Often the agents discussed have not been approved for these indications by the US Food and Drug Administration (FDA), but they are commonly used for them anyway. Conversely, many FDA indications that the antibiotics do have are not listed here, because they are often out-of-date. For example, FDA does not change indications when resistance makes a drug useless for an indication.

Don't Forget!

In this section, we list points that are often overlooked or especially important when dealing with the drug class.

As you read this book, try to think of situations in which the antibiotics would be useful to your patients. Think of *why* an antibiotic is useful for an indication; don't just learn *that* it is. It is our sincere hope that you, too, have that magic moment where the world of antibiotics and the study of infectious diseases click together. Let us know when it happens.

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NEW TO THE *FIFTH EDITION*

The fifth edition of *Antibiotics Simplified* expands on the drug classes covered in the previous editions while retaining the “key point” focus of the text that has made it successful. Availability of drugs as intravenous and/or oral formulations has been added. The *Fifth Edition* includes coverage of new agents, including the rapidly changing world of antiviral pharmacotherapy. A flurry of new antibiotics have been approved (and added) since the *Fourth Edition*, and the chapters for each class were updated with new clinical and scientific findings. Unavailable drugs have been removed, resulting in the demise of Conan’s least favorite section: antipseudomonal penicillins.

PART 1

CONSIDERATIONS WITH ANTIBIOTIC THERAPY

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1
THE WONDERFUL WORLD OF MICROBIOLOGY

Despite the promises of the household-products industry, almost *every surface* is covered in microorganisms almost *all the time*. Swab a countertop, your skin, or your dinner, and you will find a little world—and that covers only the estimated 1% of bacteria that can be cultured! Obviously, trying to sterilize our patients (and our countertops) is futile; we have to try to target the bad organisms and let the rest happily crawl all over us—they greatly outnumber our own cells in our bodies anyway.

In the microbial world, bacteria lie toward the “less like us” end of the spectrum (**FIGURE 1-1**). They are prokaryotes, not eukaryotes like fungi, protozoa, and humans. Viruses are even more different from us—they are a virus-making package of genetic instructions in a cell-attacking protein coat (**FIGURE 1-2**). Differences between cells of microorganisms and humans in anatomy, biochemistry, and affinity of antibiotics for their targets are what allow for the safe and effective use of antibiotics. In this section we will concentrate on the microbiology of bacteria. The unique characteristics of fungi, viruses, mycobacteria, and parasites will be discussed in the sections where agents active against those organisms are introduced.

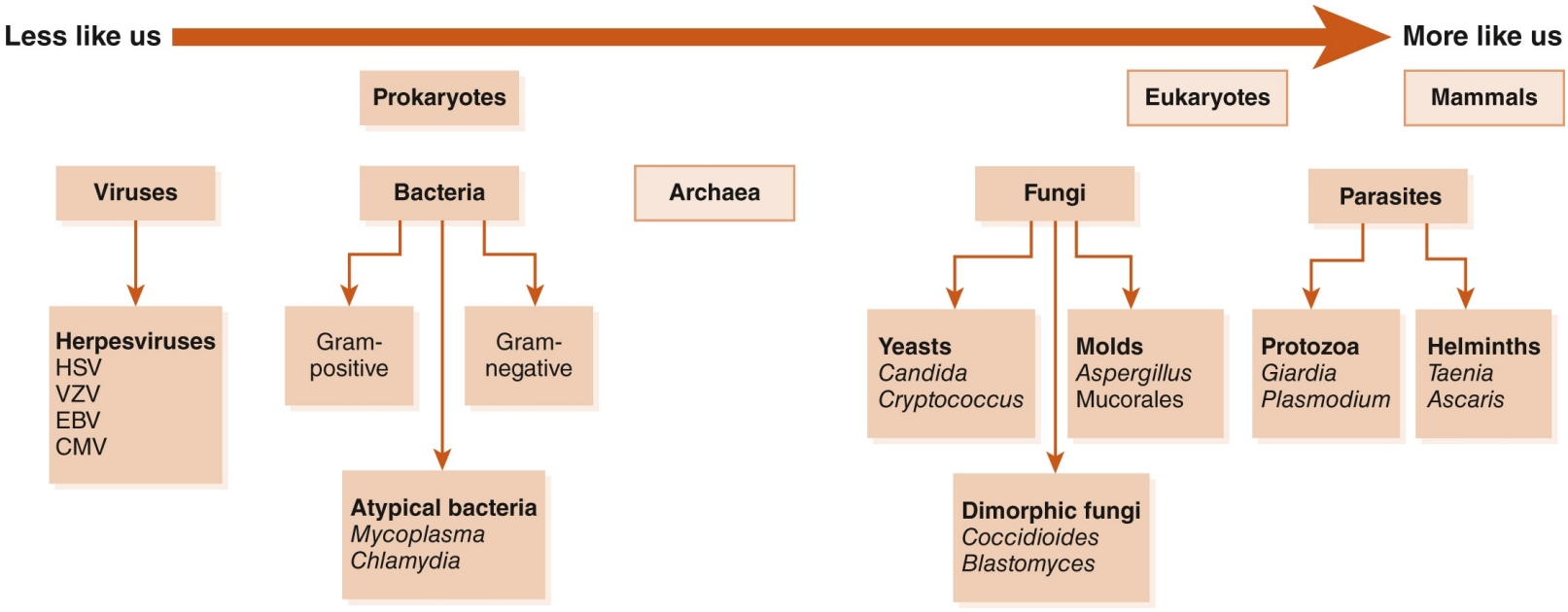

FIGURE 1-1 The Microbial World

Description

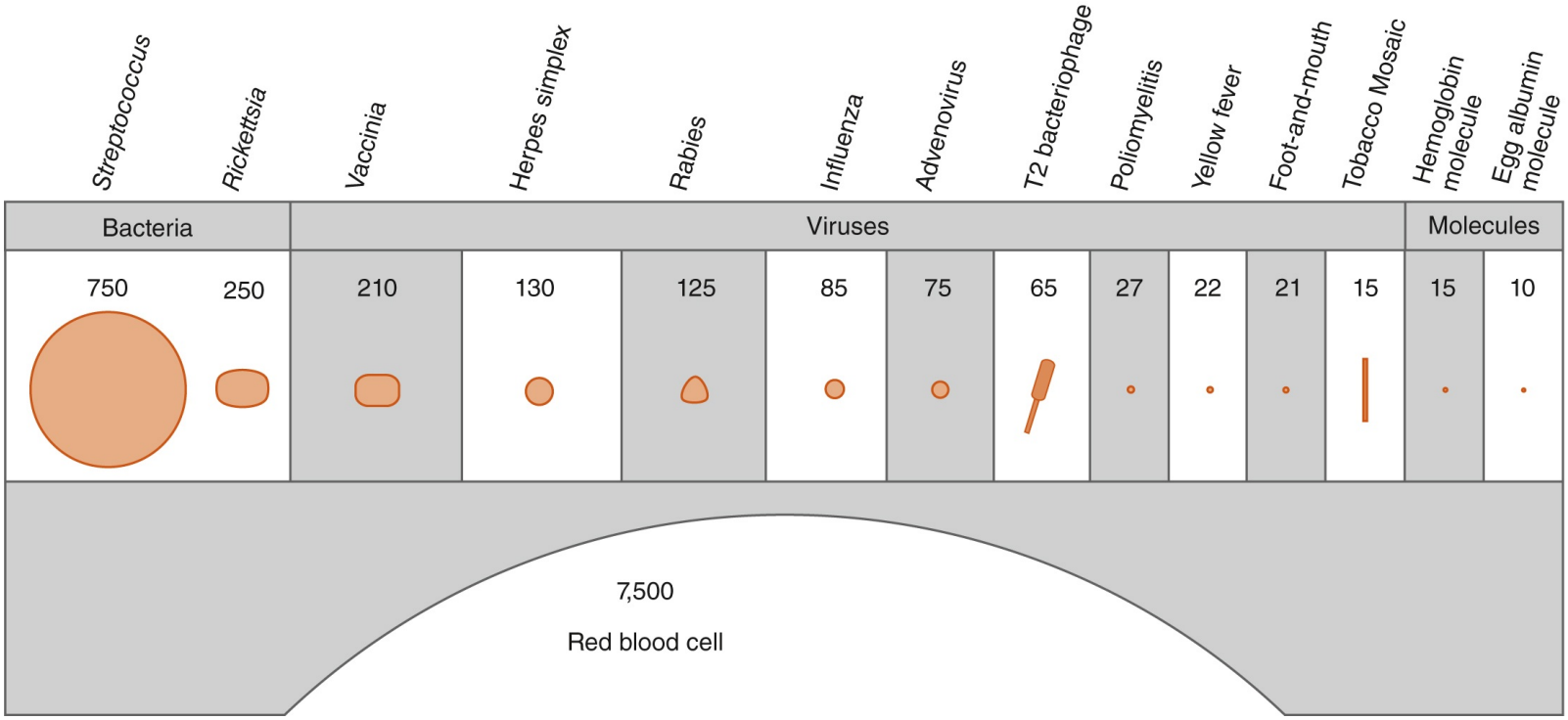

FIGURE 1-2 Relative Sizes of Microorganisms

Description

Differentiating bacteria that are responsible for infection from those just along for the ride can be difficult. Many bacteria that can cause human disease are also normal commensal flora, including *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Thus, growth of one of these organisms from a culture is not necessarily synonymous with infection. Suspicion of infection is increased greatly if the organism grows from a normally sterile site, such as the bloodstream or cerebrospinal fluid (CSF). Indicators of infection in nonsterile sites (such as sputum and wound cultures) are a high number of organisms, the presence of inflammatory cells, and symptoms referable to the culture site (e.g., cough or dyspnea in a patient with a sputum culture growing *S pneumoniae*, redness and pain in a patient with a skin culture growing *S aureus*).

Definitive identification and susceptibility testing may take anywhere from hours to months, depending on the organism and the methods used. Microscopic examination and staining may allow for rapid preliminary identification. For bacteria, the most important of these techniques is the Gram stain. Being able to interpret preliminary results of microbiology testing will allow you to provide the most appropriate therapy for your patients as early as possible. Increasingly, new tools such as polymerase chain reaction (PCR) or matrix-associated laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry are being used to provide even more rapid and precise organism identification, but these methods are not available in all settings or on all specimen types.

One of the most fundamental differences among types of bacteria is how they react to a Gram stain. Gram stain (crystal violet) is a substance that selectively stains the cell walls of gram-positive bacteria but is easily washed away from gram-negative bacteria. Why? In gram-positive bacteria, the outermost membrane is a thick layer of peptidoglycan, a cellular substance that gives bacterial cells rigidity. In contrast, gram-negative bacteria have an outer membrane of lipopolysaccharide that blocks the stain from adhering to the peptidoglycan within the cell (**FIGURE 1-3**).

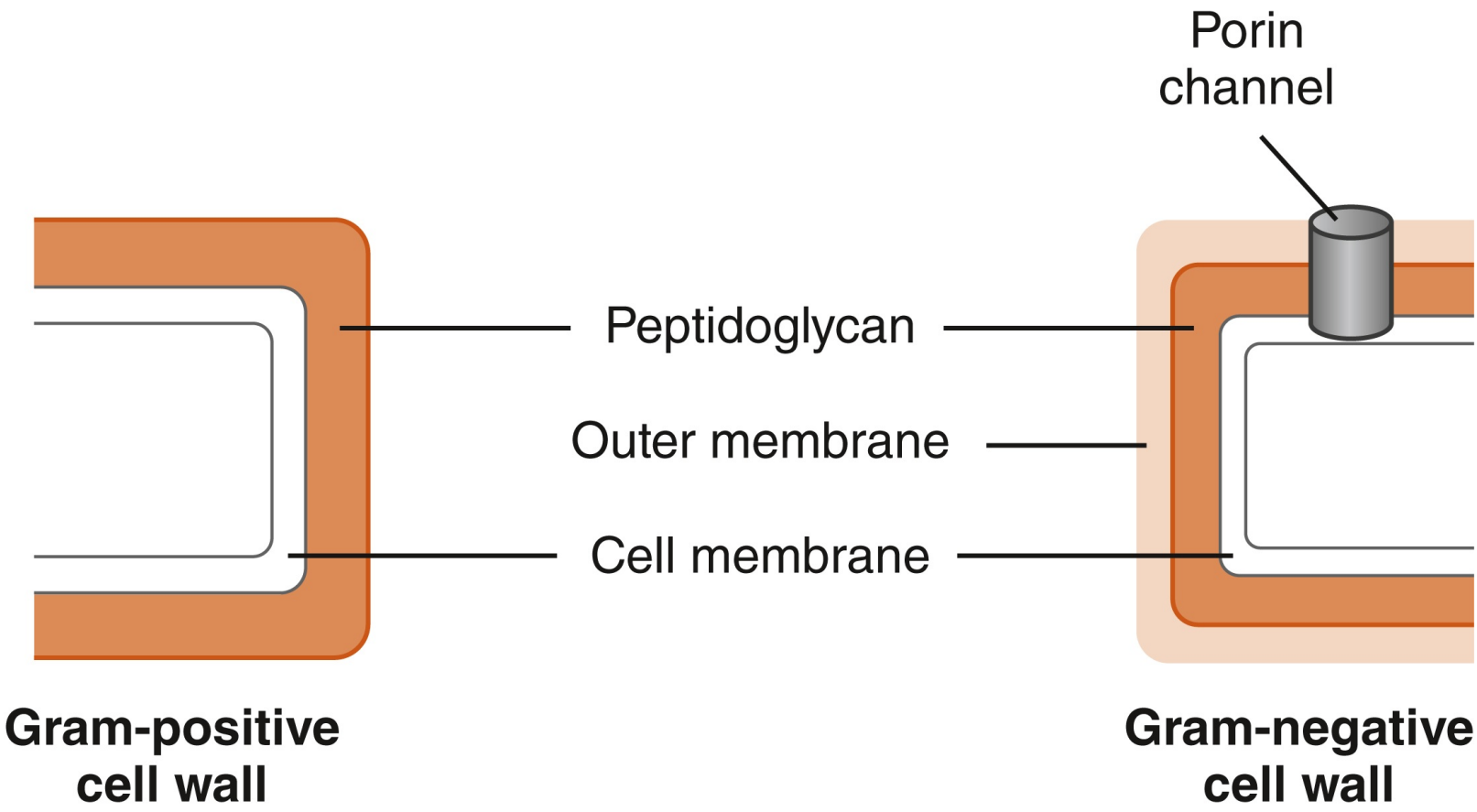

FIGURE 1-3 Cell Walls of Gram-Positive and Gram-Negative Organisms

Description

Gram-negatives also contain peptidoglycan, but in smaller amounts, and it is not the outermost layer of the cell. Both gram-positive and gram-negative organisms contain an inner cell membrane that separates the cell wall from the cytoplasm of the organism.

FIGURE 1-4 and **FIGURE 1-5** show how you can identify different bacteria by differences in morphology, oxygen tolerance, and biochemical identification.

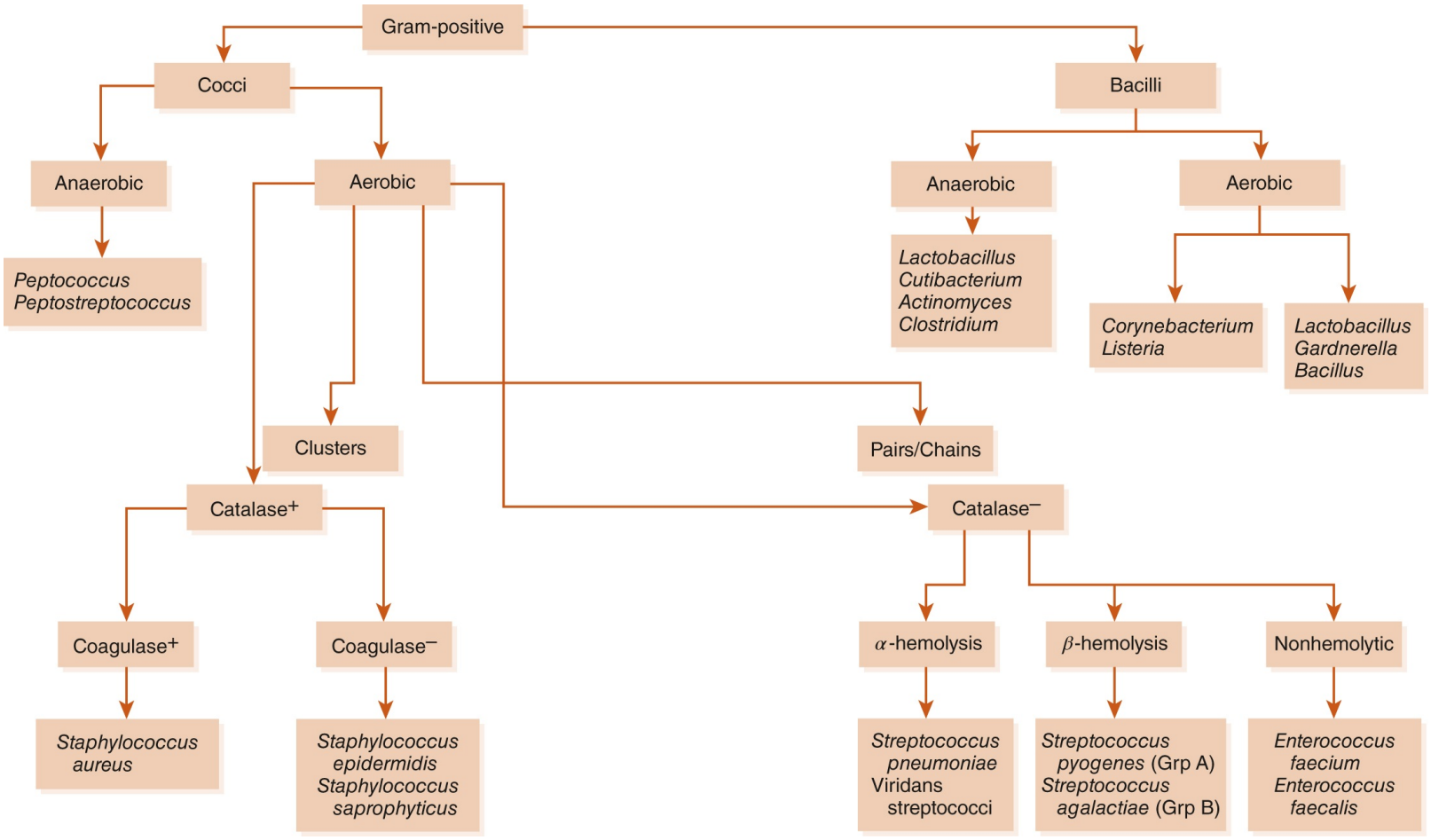

FIGURE 1-4 Gram-Positive Bacteria

Description

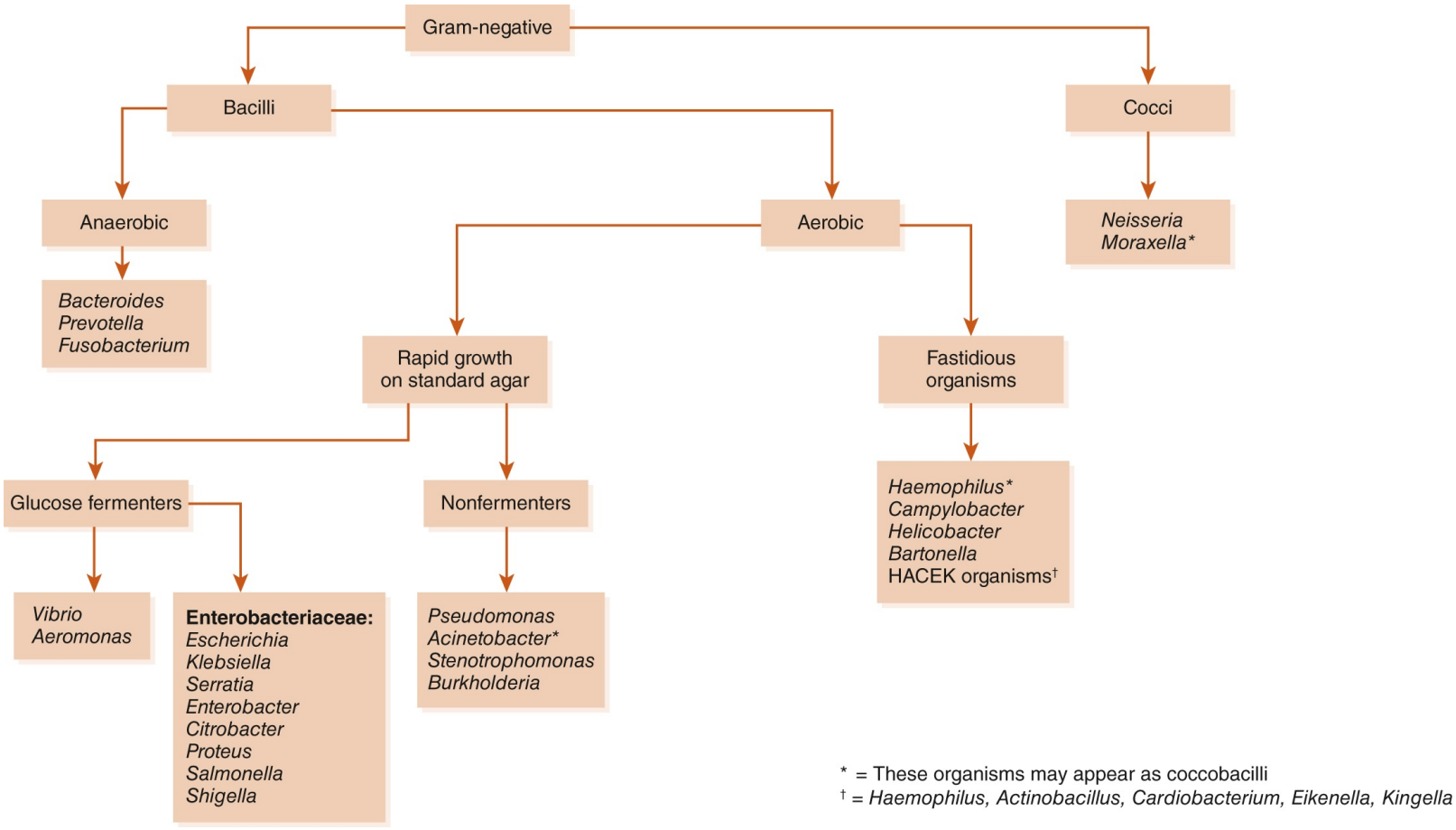

FIGURE 1-5 Gram-Negative Bacteria

Description

Rapid identification of gram-positive bacteria based on morphology and preliminary biochemical tests can help to direct therapy.

1. **Morphology:** Most medically important gram-positive pathogens are cocci (spheres) rather than bacilli (rods). The finding of gram-positive bacilli should be interpreted within the clinical context: In blood cultures, gram-positive bacilli often represent common skin contaminants (such as *Cutibacterium*, *Corynebacterium*, and *Bacillus* species), since the skin barrier must be bypassed to collect the culture. Detection of gram-positive bacilli from necrotizing wound infections suggests clostridial infection, whereas the finding of gram-positive bacilli in CSF cultures raises the concern for *Listeria*.
2. **Colony clustering:** Within the gram-positive cocci, the staphylococci tend to form clusters, whereas the streptococci and enterococci appear in pairs or chains. Again, the clinical context aids in interpretation: The finding of streptococci in a respiratory culture suggests *S pneumoniae*, whereas a report of streptococci from an intra-abdominal culture suggests *Enterococcus* (which may be identified preliminarily as a *Streptococcus*).
3. **Biochemistry and appearance on agar:** The rapid catalase test helps to differentiate staphylococci from streptococci. The coagulase test is useful for differentiating the more virulent (coagulase-positive) *S aureus* from its cousin the coagulase-negative *Staphylococcus epidermidis*. *S epidermidis* is a frequent contaminant of blood cultures; if only one of a pair of blood samples is positive for coagulase-negative staphylococci, treatment may not be required. The pattern of hemolysis (clearing around colonies on agar plates) helps to differentiate among the streptococci: the oral flora (α-hemolytic *S pneumoniae* and the viridans streptococci); pathogens of the skin, pharynx, and genitourinary tract (β-hemolytic group A and B strep); and the bugs of gastrointestinal origin (nonhemolytic enterococci: the more common *Enterococcus faecalis* and the more resistant *Enterococcus faecium*).

Preliminary identification is somewhat less useful with the gram-negative bacteria because more extensive biochemical tests are usually needed to differentiate among them.

1. **Morphology:** Among gram-negative pathogens, the bacilli predominate. The situation in which identification of gram-negative cocci is most useful is in the setting of meningitis, where this finding would strongly suggest *Neisseria meningitidis*. Note also that some organisms have an intermediate or “coccobacillary” appearance, which may suggest organisms of the genera *Haemophilus*, *Moraxella*, or *Acinetobacter*.
2. **Glucose/lactose fermentation:** Many pathogens within the order Enterobacterales (including *E coli*, *Klebsiella*, *Serratia*, and *Enterobacter*) generally ferment glucose/lactose;

at this point the lab may identify them as “enteric gram-negative rods” or “lactose-fermenting gram-negative rods.” In contrast, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, and *Burkholderia* are “nonfermenters”; a report of “nonfermenting gram-negative rods” should lead you to reassess and, if necessary, broaden your antibiotic coverage, because many of these organisms have a high level of antibiotic resistance.

3. **Fastidious organisms:** These organisms are picky eaters—they grow slowly and often require specially supplemented media. Thus, it may take a few days to a few weeks for them to grow from culture.

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2

GENERAL APPROACH TO INFECTIOUS DISEASES

The pharmacotherapy of infectious diseases is unique. In the pharmacotherapy of most diseases, we give drugs that have some desired pharmacologic action at some receptor or protein in the *patient*. To treat infections, we give antibiotics to exert a desired pharmacologic effect on the *organism* that is causing infection in the patient. With few exceptions, direct effects on the patients from antibiotics are not desired and are adverse effects. It is the third point in the triangle of infectious diseases pharmacotherapy—the pathogen—that makes each infection in each patient unique (**FIGURE 2-1**). The fact that the pharmacotherapy of infectious diseases involves organisms that change and "fight back" confuses many clinicians, but the approach to the patient with an infection is relatively simple and consistent. Understanding this approach is the first step in developing a useful expertise in infectious diseases and antibiotic use.

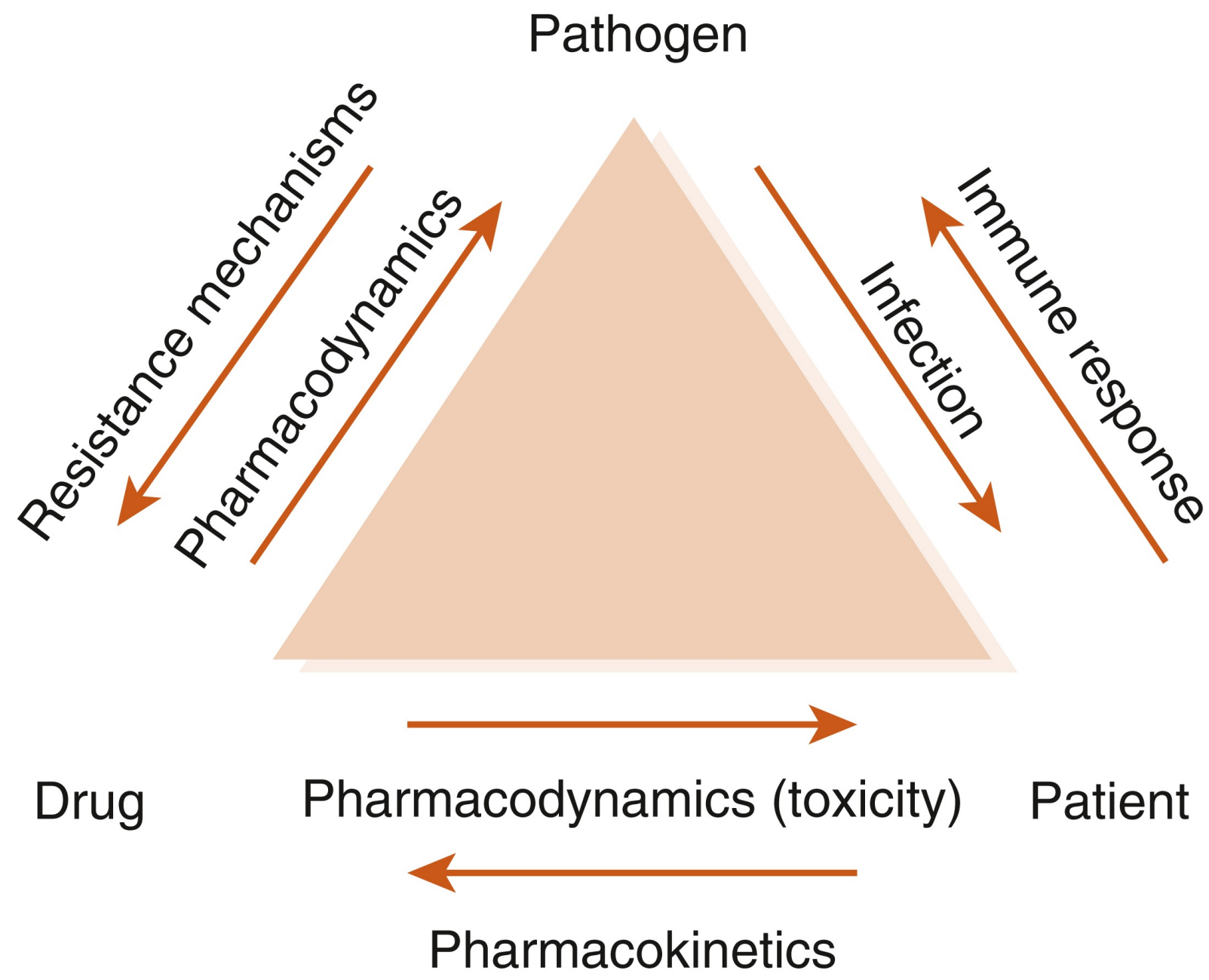

FIGURE 2-1 Relationships in the Infected Patient

Description

Note: Technically the term *antibiotic* refers only to a subset of antibacterial drugs that are natural products. The terms *antiinfective* and *antimicrobial* encompass antibacterial, antifungal, antiviral, and antiparasitic drugs. However, because *antibiotic* is the more commonly used term, we will use it to refer to antimicrobials in general or antibacterials specifically.

Prophylactic Therapy

The use of antimicrobial chemotherapy—that is, the treatment of microorganisms with chemical agents—falls into one of three general categories: prophylaxis, empiric use, and definitive therapy. *Prophylaxis* refers to antibiotics given to prevent an infection that has not yet developed. Use of prophylactic therapy should be limited to patients at high risk of developing an infection, such as those on immunosuppressive therapy, those with cancer, or patients who are having surgery. These patients have weakened natural defenses that render them susceptible to infection. Because the likelihood of infection by some types of organisms in these

patients is high and the consequences of infection are dire, we administer antimicrobial drugs to prevent infections from occurring. However, the world is not sterile, and breakthrough infections do occur among patients receiving prophylaxis. The key to understanding antimicrobial prophylaxis is to remember that patients who receive it do not have an infection, but they are at risk for one. It is also the exception, not the rule—most people do not receive antimicrobial prophylaxis against most infections.

Empiric Therapy

Empiric therapy is given to patients who have a proven or suspected infection, but the responsible organism(s) has or have not yet been identified. It is the type of therapy most often initiated in both outpatient and inpatient settings. After the clinician assesses the likelihood of an infection based on physical exam, laboratory findings, and other signs and symptoms, he or she should generally collect samples for culture and Gram staining. For most types of cultures, the Gram stain is performed relatively quickly. In the Gram stain, details about the site of presumed infection are revealed, such as the presence of organisms and white blood cells (WBCs), morphology of the organisms present (e.g., gram-positive cocci in clusters), and the nature of the sample itself, which in some cases indicates if the sample is adequate. The process of culturing the sample begins around the time that the clinician performs the Gram stain. After a day or so, testing will reveal the identification of the organism, and eventually the organism can be tested for its susceptibility to various antibiotics.

However, this process takes several days, so empiric therapy is generally initiated *before* the clinician knows the exact identification and susceptibilities of the causative organism. Empiric therapy is our best guess of which antimicrobial agent or agents will be most active against the likely cause of infection. Sometimes we are right, and sometimes we are wrong. The significance of making a correct guess differs depending on the severity of the infection; a wrong choice for an uncomplicated urinary tract infection (UTI) results in an annoyed patient, whereas the wrong choice for meningitis is fatal. Keep in mind that empiric therapy should not be directed against every known organism in nature—just those that cause the infection in question. In other words, broad-spectrum antibiotics are not a substitute for rational thought!

Definitive Therapy

After culture and sensitivity results are known, the *definitive therapy* phase of treatment can begin. Unlike empiric therapy, with definitive therapy we know on what organisms to base our treatment and which drugs should work against them. At this phase, it is prudent to choose antimicrobial agents that are safe, effective, narrow in spectrum, and cost-effective. This helps us avoid unneeded toxicity, treatment failures, and the possible emergence of antimicrobial resistance; it also helps manage costs. In general, moving from empiric to definitive therapy involves decreasing the spectrum of coverage, because we do not need to target organisms that are not causing infection in our patient. In fact, giving overly broad-spectrum antibiotics can lead to the development of superinfections: infections caused by organisms resistant to the anti-biotics in use that occur during therapy.

The clinician who is treating an infected patient should always strive to make the transition to definitive therapy. Although it seems obvious, this frequently does not occur. If the patient

improves on the first antibiotic, clinicians may be reluctant to transition to more narrow-spectrum therapy. Also, some infections may resolve with empiric therapy before culture results would even be available, as frequently happens with uncomplicated UTIs. In other cases, cultures may not be obtained or may be negative in spite of strong signs that the patient has an infection (e.g., clinical symptoms, fever, increased WBC count). Outpatient clinicians frequently skip the culture collection step, begin empiric therapy, and wait to see what happens. This may be because of time pressures or the perceived cost and inconvenience of obtaining cultures in patients with low-acuity infections. In many situations it is important that clinicians continuously consider the need to transition to definitive therapy. Overly broad-spectrum therapy has consequences, and the next infection is likely to be harder to treat. Excessive empiric antibiotic use is a big part of the reason there is an antimicrobial resistance crisis. Keep in mind the general pathway for the treatment of infectious diseases shown in **FIGURE 2-2**.

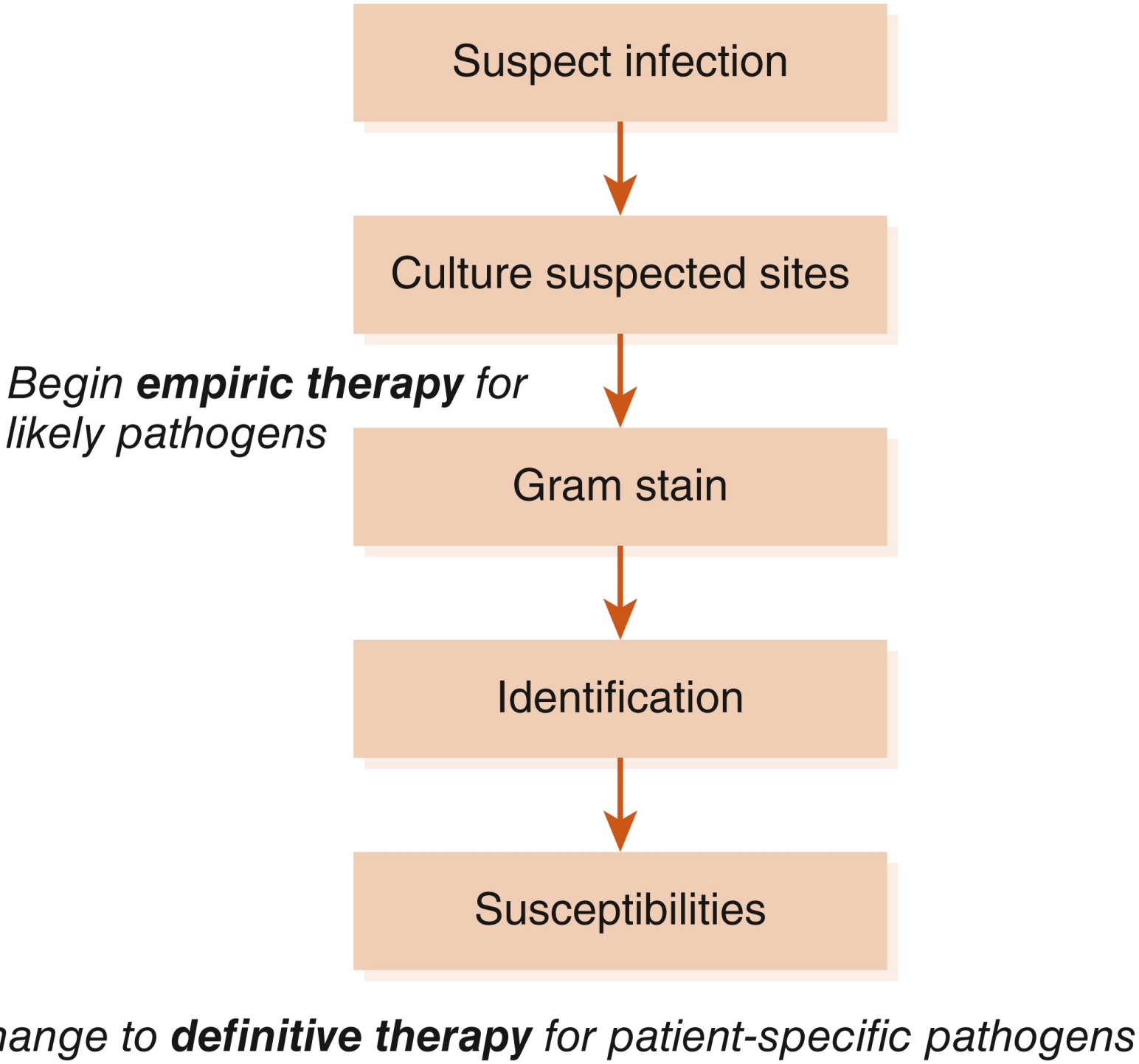

FIGURE 2-2 General Approach to Infectious Diseases

Description

Examples of Therapy

Here are a few examples of each type of therapy:

Prophylaxis Therapy

- Trimethoprim/sulfamethoxazole (TMP/SMX) to prevent *Pneumocystis jirovecii* pneumonia in a patient on cyclosporine and prednisone after a liver transplant
- Letermovir to prevent CMV infection in a patient who received a stem cell transplant
- Cefazolin given before surgery to prevent a staphylococcal skin infection of the surgical site

Empiric Therapy

- Levofloxacin initiated for a patient with presumed community-acquired pneumonia
- Ceftriaxone given for the treatment of suspected pyelonephritis
- Voriconazole initiated for a neutropenic bone marrow transplant patient with shortness of breath and a radiograph suggestive of pulmonary aspergillosis
- Vancomycin, tobramycin, and meropenem for a patient with probable ventilator-associated pneumonia in the intensive care unit

Definitive Therapy

- Transitioning from piperacillin/tazobactam to ampicillin in a patient with a wound infection caused by *Enterococcus faecalis*, which is susceptible to both drugs
- Discontinuing ceftriaxone and initiating ciprofloxacin for a patient with a UTI caused by *Klebsiella pneumoniae* that is resistant to ceftriaxone but susceptible to ciprofloxacin
- Stopping caspofungin and initiating fluconazole for an improving patient with *Candida* in a blood isolate when the species is identified as *Candida albicans* (which is generally susceptible to fluconazole)
- Narrowing therapy from vancomycin, ciprofloxacin, and meropenem to linezolid alone for a patient with hospital-acquired pneumonia whose deep respiratory culture grew only methicillin-resistant *Staphylococcus aureus* (MRSA) that is susceptible to linezolid

Case Study

Here is an example of treating a patient with an infection by the above pathway:

> TR is a 63-year-old man with a history of diabetes, hypertension, and coronary artery disease who comes to the hospital complaining of pain, redness, and swelling around a wound on his foot. Close inspection reveals that he has an infected

diabetic foot ulcer. He is admitted to the hospital (Day 1). A surgeon performs surgical debridement that evening and sends cultures from the wound during surgery as well as blood cultures. Another clinician initiates *empiric therapy* with vancomycin and ertapenem.

On Day 2, Gram stain results from the wound are available. There are many WBCs with many gram-positive cocci in clusters but no gram-negative rods (GNRs), so the clinician discontinues ertapenem. Blood cultures do not grow any organisms.

The following day (Day 3), culture results from the wound reveal many *S aureus*. Because vancomycin is usually effective against this organism, its use is continued.

On Day 4, susceptibility results from the wound culture return. The *S aureus* is found to be susceptible to methicillin, oxacillin, cefazolin, clindamycin, TMP/SMX, and vancomycin. It is resistant to penicillin, ampicillin, tetracycline, and levofloxacin. Because the isolate from TR's wound is methicillin-susceptible *S aureus* (MSSA), the clinician discontinues vancomycin and initiates *definitive therapy* with cefazolin. As TR improves towards discharge, the cefazolin is changed to oral cephalexin.

Note how in TR's case we began empiric therapy with a broad-spectrum regimen of vancomycin and ertapenem to cover the gram-positive and gram-negative aerobes and anaerobes that tend to cause diabetic foot infections but narrowed that therapy over time as Gram stain and culture data returned. Eventually we were able to choose a highly effective, narrow-spectrum, inexpensive, and safe choice of definitive therapy that was driven by microbiology results. Both vancomycin and ertapenem were active against TR's *S aureus* as well, but both represent less-ideal therapy choices, as ertapenem is broader in spectrum and vancomycin's anti-MRSA activity is not needed. Note: Ertapenem and cephalexin's activity against this isolate is inferred from the susceptibility pattern even though susceptibility to these agents was not tested directly.

A Note on Rapid Diagnostics

Novel ways to determine the identification of microorganisms are making their way into clinical practice. Identification of bacteria rapidly by mass spectroscopy has become common in microbiology laboratories, decreasing time from isolation to identification. Techniques that do not rely on culturing and the inherent delay that it represents are already commonly used to detect and quantify many viruses, such as polymerase chain reactions (PCR). These and other techniques are being used to identify other pathogens as well, such as strains of *Candida* (to determine likely fluconazole susceptibility), *Clostridioides difficile*, and even MRSA. As these technologies permeate clinical microbiology labs, hopefully the delays to effective therapy that current gold-standard culture and susceptibility testing cause will vanish.

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3
ANTIBIOTIC PHARMACOKINETICS

The term *antibiotic pharmacokinetics* refers to *how* (and to *what extent*) antibiotics *enter the body*, *where they go* once they are *inside*, and *how they get out*. These three phases of pharmacokinetics are usually described as *absorption*, *distribution*, and *metabolism/excretion* (often abbreviated ADME). The pharmacokinetics of antibiotics are key to the effectiveness of the drugs in clinical practice; there is no benefit for a patient to receive an antibiotic that is great at killing bacteria on a petri dish if it never gets to the site of the infection at a high enough concentration to work. If you think about it, this is an issue for most types of human disease, but in infectious diseases it is very relevant clinically. You do not have to wonder if phenytoin distributes to the central nervous system (CNS)—it does, or else it would be worthless for seizures. However, if you are treating a brain abscess, it is important to know that metronidazole distributes there well but clindamycin does not. **FIGURE 3-1** illustrates ADME phases on a concentration–time curve, with the concentration of the drug on the y-axis and the time since drug administration on the x-axis. It also indicates the key pharmacokinetic parameters of peak concentration, trough concentration, and area under the curve (AUC).

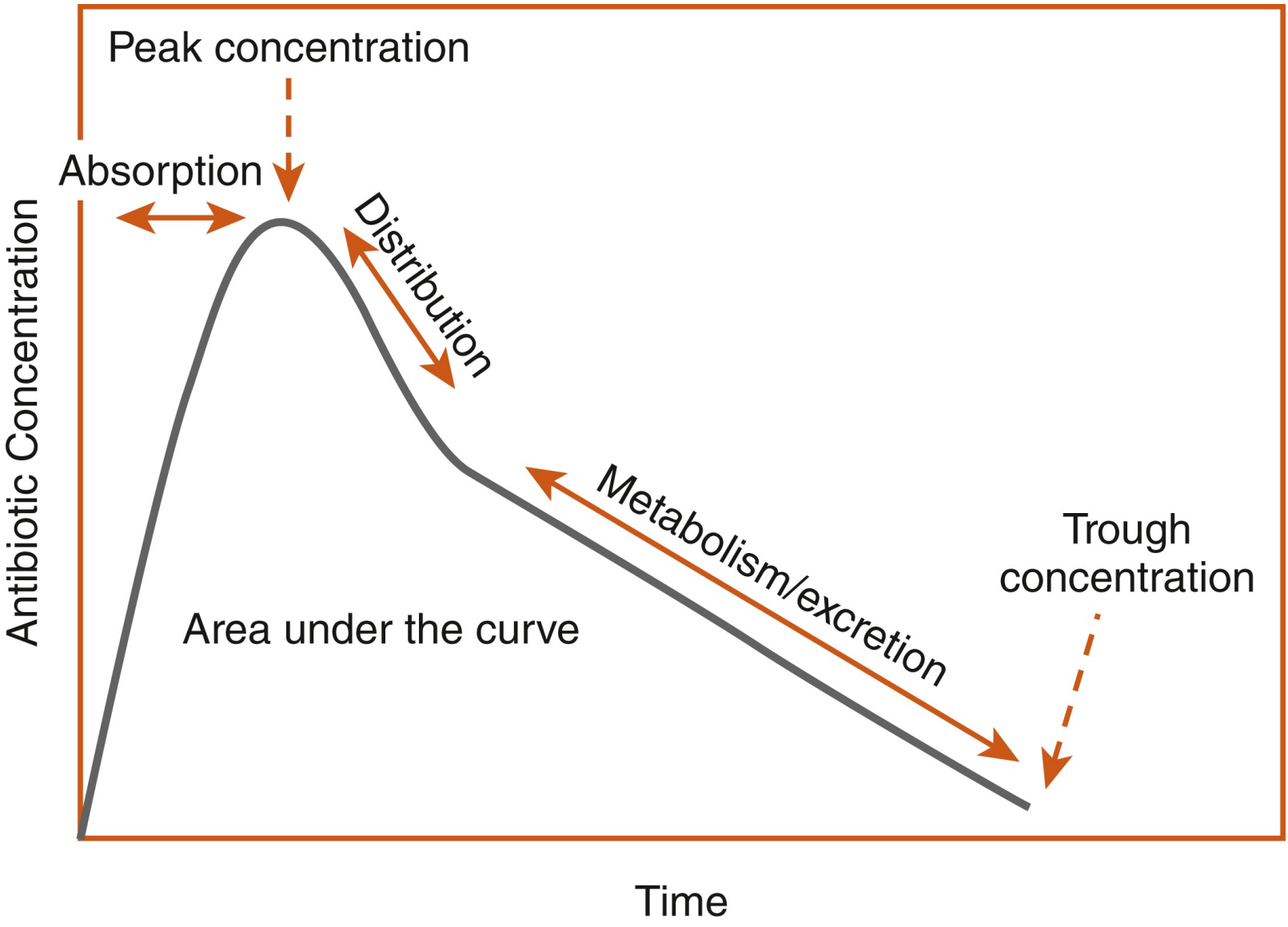

FIGURE 3-1 Pharmacokinetic Phases and Parameters

Description

Absorption

Although the term *absorption* can be applied to any route of administration (e.g., absorption from intramuscular injection or inhalation), usually it is used to refer to the uptake of orally administered drugs into the bloodstream. The percentage of a non-intravenously administered drug that enters the bloodstream (such as an oral drug), relative to an intravenous formulation of the same drug, is termed the *bioavailability*. Antibiotics with oral formulations differ substantially in their bioavailability. For some antibiotics, bioavailability is at or near 100%; the same dose administered orally or intravenously will achieve similar levels. It is worth considering that several antibiotics have very good bioavailability, but their oral doses are substantially lower than the intravenous doses. This is usually because high oral doses lead to excessive gastrointestinal (GI) tract toxicity. **TABLE 3-1** groups antibiotics into groups with high oral bioavailability and full or near intravenous–oral dose equivalence, those with good oral bioavailability but substantially lower oral than intravenous doses, and those with limited oral bioavailability. Some oral antibiotics have almost zero bioavailability and take advantage of this clinically to eradicate pathogens in the GI tract, where they achieve much higher concentrations than they would if given intravenously.

TABLE 3-1 Examples of Absorption for Different Oral Antibiotics

Drug	Bioavailability	Typical Intravenous Dose	Typical Oral Dose
Drugs with High Bioavailability and Similar Intravenous–Oral Doses			
Metronidazole	95–100%	500 mg IV q8h	500 mg po q8h
Levofloxacin	95–100%	500–750 mg IV q24h	500–750 mg po daily
Linezolid	95–100%	600 mg IV q8h	600 mg po q12h
Fluconazole	95–100%	200–400 mg IV daily	200–400 mg po daily
Doxycycline	95–100%	100 mg IV q12h	100 mg po q12h
Ciprofloxacin	~80%	400 mg IV q12h	500 mg po q12h
Drugs with High Bioavailability but Different Intravenous–Oral Doses			
Aminopenicillins	~90%	Ampicillin: 1–2 g IV q4–6h	Amoxicillin: 500 mg–1 g po tid
First-generation cephalosporins	~90%	Cefazolin: 1–2 g IV q8h	Cephalexin: 500 mg po qid
Drugs with Low Bioavailability and Different Intravenous–Oral Doses			
Cefuroxime	~40%	750 mg IV q8h	500 mg po bid
Acyclovir	~25%	5 mg/kg IV q8h	400 mg po tid

Description

It is important to consider factors that can affect the bioavailability of antibiotics. Three factors that can substantially influence absorption are food, gastric acidity, and chelating agents. Some antibiotics are better absorbed with food and some without, whereas for most the presence of food has minimal effect.

A small group of antibiotics are highly dependent on gastric acidity for adequate absorption; it is important to avoid concomitant use of drugs that raise gastric pH (antacids, proton pump inhibitors, histamine-2 receptor antagonists) when patients are started on these drugs. Finally, two key classes of antibiotics—the tetracyclines and fluoroquinolones—can bind to coadministered minerals present in the gut, such as calcium, iron, aluminum, and zinc. Administering these drugs along with mineral or some vitamin supplements can substantially reduce absorption. **TABLE 3-2** provides examples of antibiotics for which these factors need to be accounted.

TABLE 3-2 Examples of Antibiotics Whose Absorption Is Significantly Affected by Other Factors

Absorption Improved with Food	Absorption Impaired by Food	Absorption Impaired by Drugs That Increase Gastric pH	Absorption Impaired by Minerals
Posaconazole suspension	Voriconazole	Itraconazole	Fluoroquinolones
Itraconazole capsules	Itraconazole solution	Posaconazole suspension	Tetracyclines
Atazanavir	Omadacycline	Atazanavir	Bictegravir
Darunavir	Rifampin	Rilpivirine	Dolutegravir
Rilpivirine	Isoniazid		
	Pyrazinamide		

Description

Distribution

After a drug is absorbed or injected into the bloodstream, it moves into various tissues (e.g., bone, cerebrospinal fluid, lungs), a process known as *distribution*. The concentrations in these tissues can be similar to, lower than, or greater than the concentration of the antibiotic in the blood. A consequence is that a drug may be more or less effective in a particular tissue than would be expected based on its concentrations in the blood. For example, the concentrations of antibiotics in the cerebrospinal fluid are commonly much lower than their bloodstream concentrations, limiting the effectiveness of many antibiotics in the treatment of meningitis. On the other hand, the macrolide antibiotics are more effective in lung infections than may be anticipated based on their blood levels, because they concentrate in pulmonary macrophages. With a few exceptions, such as cerebrospinal fluid, it is difficult to obtain samples of human tissues to determine antibiotic concentrations, and it is technically difficult to measure the concentrations in tissues like bone. Thus, data on drug distribution are often extrapolated from animal models, which may or may not be good surrogates for humans.

The extent to which antibiotics distribute into different tissues is largely determined by the physicochemical properties of the drug (lipophilicity, charge, molecular size, etc.). A key determinant of distribution is the degree to which an antibiotic binds to proteins in the bloodstream, most importantly albumin. A drug bound to proteins is not able to diffuse across membranes into different tissues; thus, antibiotics that are highly protein bound *may* be less likely to reach effective concentrations in certain tissues (such as the CNS). It is important to realize that the percentage degree of penetration of an antibiotic into a tissue is not the only determinant of effectiveness in that tissue. For example, ceftriaxone is a very highly protein-bound drug, and 5% or less enters into the CNS in patients with meningitis. However, large doses (2 g twice daily in adults) of ceftriaxone can be given safely to adults, resulting in high serum levels (peak levels of around 200 mg/L). In addition, the minimum inhibitory concentration (MIC) to ceftriaxone for organisms usually causing meningitis is typically very low (1 mg/L or less); thus, a concentration far in excess of the organism's MIC can be obtained (200 mg/L × 5% = 10 mg/L). Also, the concentration–time curves in many tissues are different than they are in the bloodstream—more like rolling hills than peaks and valleys. (Think—Appalachians versus the Rockies.)

Patient characteristics may also significantly influence drug distribution. In order for a drug to distribute to a tissue, there must be adequate blood flow to that tissue. Conditions that reduce blood flow to tissues, either locally (e.g., peripheral vascular disease) or systemically (septic shock), can reduce antibiotic concentrations at the site of infection. Patients with severe

infections can develop abscesses or areas of dead and devitalized tissue; distribution of antibiotics into these “protected” sites of infection can be significantly impaired. These patients are perfect setups for treatment failure and development of resistance and highlight the importance of appropriate surgical management of infections along with antibiotic treatment. Given the growing problem of obesity, another important consideration is the extent to which drugs distribute into adipose tissue. Depending on the characteristics of the drug, it is possible to underdose patients who are morbidly obese (if the drug distributes extensively into adipose tissue and doses for standard weights are used) or overdose them (if a higher dose is used because of obesity, but the drug does not distribute well into excess adipose tissue). Thus, you may see recommendations for antibiotic dosing based on *total or actual* body weight, *ideal* body weight (an estimate of the patient’s body weight without their excess adipose tissue), or *adjusted* body weight (a value between the ideal and total body weight). This is an area that is relatively understudied.

Finally, it is important to note that with few exceptions, microbiological susceptibility testing does not account for distribution and is based on *achievable bloodstream concentrations*. For example, the microbiology lab may determine that an organism with an MIC of 4 mg/L is considered susceptible to a drug that achieves a concentration of 8 mg/L in the bloodstream, but it may only achieve a concentration of 1 mg/L in cerebrospinal fluid. Thus, that drug is likely to work for a bloodstream infection caused by the organism but would fail for meningitis, where cerebrospinal fluid concentrations are important. Thus, distribution is a key consideration when choosing antibiotics.

Metabolism/Excretion

Many antibiotics are excreted from the body, either in the urine or feces, in the same form as they were administered. In fact, shortly after penicillin was developed and supplies were scarce, physicians used to collect the urine of patients who received penicillin and recrystallize the drug for use in other patients! When a drug is excreted unchanged, it can reach very high concentrations in the area in which it is eliminated, making it potentially more effective for infections in those systems than would be anticipated based on blood concentrations. For example, the concentrations of nitrofurantoin achieved in the blood and tissues are inadequate to inhibit bacterial growth. However, it is removed from the bloodstream by the kidneys and accumulates in the bladder until its, ahem, final clearance. The concentrations achieved in the bladder are manyfold higher than those in the bloodstream, making nitrofurantoin an effective drug for treatment of bladder infections.

When the body does not inactivate the drug, an important consideration is to appropriately reduce the administered dose of the drug if there is damage to the organ responsible for excreting the drug. The most common example of this for antibiotics is the need to reduce the doses of most beta-lactams for patients with kidney dysfunction to avoid accumulation of toxic levels of the drug. Practitioners also need to be vigilant to increase doses if patients have improving renal function, such as after acute renal failure, or treatment failure may occur.

Other drugs may be extensively transformed by the body prior to their excretion. These antibiotics that undergo extensive metabolism are considered to be *substrates* of drug-metabolizing enzymes. They have the potential to be subject to clinically important drug interactions, as other drugs may interfere with the enzymes that break down the drugs.

Moreover, certain antibiotics have the potential to influence the metabolism of other drugs, either through *inhibition* of those enzymes (leading to a decrease in metabolism of the other drug) or *induction* (leading to an increase in metabolism of the other drug). A list of antibiotics with the greatest likelihood of clinically significant metabolic drug interactions is in **TABLE 3-3**, organized by whether the drug is a substrate, an inhibitor, or an inducer. (Note that drugs may be in more than one category.) Several antibiotic classes are particularly prevalent: macrolides, azole antifungals, antituberculosis drugs, and antiretrovirals account for most of the antibiotics with significant drug interactions. Complex drug interactions can occur with these drugs; for example, the antiretroviral drug etravirine is simultaneously a substrate, an inhibitor, and an inducer of drug-metabolizing enzymes!

TABLE 3-3 Examples of Antibiotics with Significant Metabolic Drug Interactions

Substrates	Inhibitors	Inducers
Erythromycin	TMP/SMX	Rifampin
Clarithromycin	Metronidazole	Rifabutin
Eravacycline	Fluconazole	Efavirenz
Atazanavir	Voriconazole	Nevirapine
Darunavir	Itraconazole	Etravirine
Efavirenz	Posaconazole	
Elvitegravir	Erythromycin	
Maraviroc	Clarithromycin	
Rilpivirine	Ritonavir	
Voriconazole	Cobicistat	
	Etravirine	

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4
ANTIBIOTIC PHARMACODYNAMICS

The term *antibiotic pharmacodynamics* refers to the manner in which antibiotics interact with their target organisms to exert their effects: Does the antibiotic kill the organism or just prevent its growth? Is it better to give a high dose of antibiotics all at once or to achieve sustained concentrations for a longer time? Clinicians increasingly recognize such considerations as important in maximizing the success of therapy, especially for difficult-to-treat infections and in immunocompromised patients.

Susceptibility Testing

Typically, one judges the susceptibility of a particular organism to an antibiotic based on the minimum inhibitory concentration (MIC) for the organism–antibiotic combination. Classically, the microbiology laboratory determines the MIC by combining a standard concentration of the organism that the patient has grown with increasing concentrations of the antibiotic. Historically this was done in test tubes (**FIGURE 4-1**), but today it is done more commonly on microdilution plates or with automated systems. The mixture is incubated for about a day, and the laboratory technician examines the tubes or plates (with the naked eye or with a computer) for signs of cloudiness, indicating growth of the organism. The mixture with the *lowest concentration* of antibiotic where there is *no visible growth* is deemed to be the MIC. For each organism–antibiotic pair, there is a particular cutoff MIC that defines susceptibility. This particular MIC is called the *breakpoint*. **TABLE 4-1** provides examples of how breakpoints differ for various organism/pathogen combinations and even based on the site of infection. Note that just because an antibiotic has the lowest MIC for a pathogen it does not mean it is the best choice

—different antibiotics achieve different concentrations in the body in different places. Thus, antibiotic MICs for a single organism generally should not be compared across different drugs in selecting therapy.

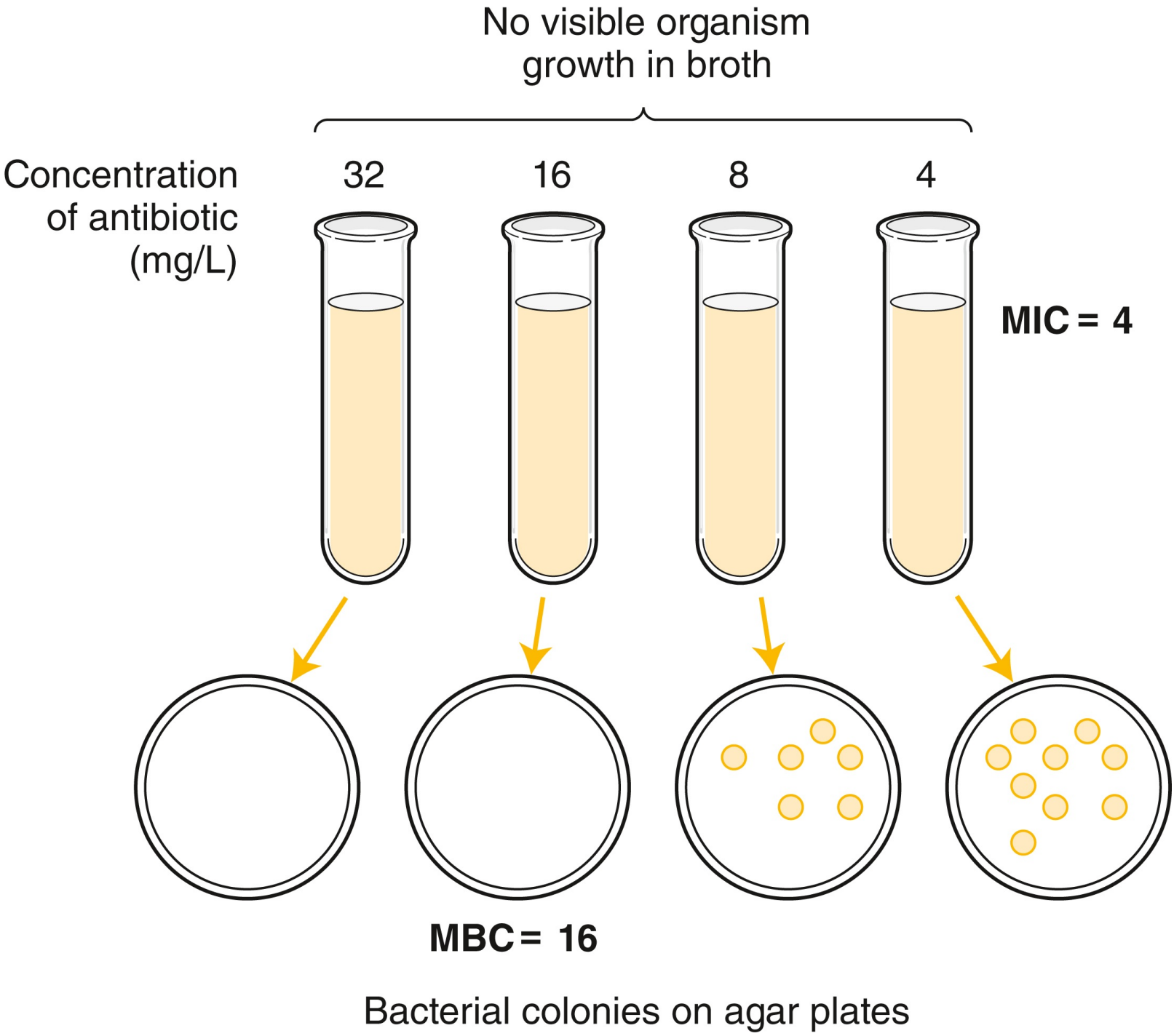

FIGURE 4-1 Susceptibility Testing of Antibiotics

Description

TABLE 4-1 | **Examples of Antibiotic Susceptibility Breakpoints**

Organism Antibiotics	Susceptible (Breakpoint)	Susceptible, Dose-Dependent	Intermediate	Resistant
Escherichia Coli				
Ampicillin	≤ 8 mg/L	_	16 mg/L	≥ 32 mg/L
Cefepime	≤ 2 mg/L	4–8 mg/L	–	≥16 mg/L
Levofloxacin	≤ 0.5 mg/L	_	1 mg/L	≥ 2 mg/L
Trimethoprim/sulfamethoxazole	≤ 2/38 mg/L	_	–	≥ 4/76 mg/L
Streptococcus pneumoniae				
Ampicillin	–	_	–	–
Cefepime (meningitis) (Nonmeningeal)	≤ 0.5 mg/L ≤ 1 mg/L	_ _	1 mg/L 2 mg/L	≥2 mg/L ≥ 4 mg/L
Levofloxacin	≤ 2 mg/L	_	4 mg/L	≥ 8 mg/L
Trimethoprim/sulfamethoxazole	≤ 0.5/9.5 mg/L	_	1–2/19–38 mg/L	≥ 4/76 mg/L

Data from Clinical and Laboratory Standards Institute, M100 document, 31st edition

Description

MIC values are often misinterpreted by clinicians who are trying to choose the best therapy for their patients but may inadvertently ignore pharmacokinetic and pharmacodynamic differences between agents. For example, in Table 4-1, note that the breakpoint for levofloxacin against *E coli* is 0.5 mg/L and for ampicillin 8 mg/L. So, if an isolate of *E coli* in the bloodstream of a patient has an MIC of 0.5 mg/L to levofloxacin but 2 mg/L to ampicillin, it does not mean that levofloxacin is a better choice for that patient. Levofloxacin is a concentration-dependent drug that is typically dosed in amounts of 500–750 mg daily. Ampicillin is a time-dependent drug that is typically dosed as 1–2 g every 4–6 hours. The much higher concentrations of ampicillin achieved in the body (due to higher doses) mean that organisms with a higher MIC to ampicillin are still susceptible to it. In other words, the two numbers are not directly comparable. In fact, if the MIC were 8 mg/L to both drugs, the organism would be considered resistant to levofloxacin and susceptible to ampicillin.

Also note in Table 4-1 the categories of “susceptible,” “susceptible, dose-dependent,” “intermediate,” and “resistant.” “Susceptible” and “resistant” are self-explanatory, but what do the other terms mean? “Intermediate” is a poorly defined range where successful therapy may be possible in some circumstances, such as when the drug is eliminated renally (for a urinary tract infection) or if higher dosing is given. It is more of a gray area made to separate the two more definitive terms than a scientifically derived definition. “Susceptible, dose-dependent” is just what it sounds like—the organism may be susceptible to high doses of the drug, but treatment with low doses is likely to fail. This category was created because many of these drugs are used in various doses, and a low dose of cefepime (like 1 g IV q12h) may be enough to treat an *E coli* infection with an MIC of 2 mg/L, but a dose like 2 g IV q12h may be needed if the MIC is 4 mg/L. These may all sound like hard-and-fast rules, but they are really probabilities of how *most patients* will fare when faced with a certain bug–drug combination for their infections. Some will succeed even with high MICs, and some will fail even with low MICs.

Finally, be aware that other methods of susceptibility testing exist, including disk diffusion and gradient test strips (e.g., Etests), but that broth dilution methods are generally considered the

gold standard.

Static Versus Cidal

At the MIC the antibiotic is inhibiting growth, but it may or may not actually be killing the organism. Antibiotics that inhibit growth of the organism without killing it are termed *bacteriostatic* (or *fungistatic* in the case of fungi). If antibiotics are removed, the organisms can begin growing again. However, bacteriostatic antibiotics are usually successful in treating infections because they allow the patient's immune system to "catch up" and kill off the organisms. (Remember, many bacteria can double every 20–30 minutes!) Other antibiotics are considered *bactericidal*; their action kills the organisms without any help from the immune system.

For most infections, outcomes using appropriate bacteriostatic versus bactericidal drugs are similar; however, for certain infections, bactericidal drugs are preferred. Such infections include endocarditis, meningitis, and infections in neutropenic patients. The immune system may not be as effective in fighting these infections because of the anatomic location or the immunosuppression of the patient. Bactericidal activity is determined by taking a sample of the broth at various concentrations and below and spreading the broth on agar plates (Figure 4-1). The bacterial colonies on the plates are counted, and the concentration corresponding to a 99.9% reduction (3-log) in the original bacterial inoculum is considered to be the minimum bactericidal concentration (MBC). When the MBC is four times or less than the MIC, the drug is considered to be bactericidal; if the MBC/MIC ratio is greater than four, the drug is considered bacteriostatic. MIC testing is standard in most laboratories; MBC testing is more difficult and is not commonly done in clinical practice. **TABLE 4-2** lists drugs and indicates whether they are generally considered bacteriostatic or bactericidal; however, it should be noted that this activity can vary based on the pathogen being treated, the dose, and the growth phase of the organism.

TABLE 4-2 Antibiotic Pharmacodynamic Parameters

Antibiotic Class	Cidal or Static	Predictive PK/PD Parameter
Penicillins Cephalosporins Carbapenems Monobactams	Bactericidal	Time > MIC
Vancomycin	Bactericidal (slowly)	AUC/MIC
Fluoroquinolones Aminoglycosides Metronidazole Daptomycin	Bactericidal	AUC/MIC
Macrolides Tetracyclines Linezolid	Bacteriostatic	AUC/MIC

Pharmacokinetic/Pharmacodynamic Relationships

Besides differing in whether they kill microorganisms or merely inhibit their growth, antibiotics also differ in how they manifest their effects over time. Careful studies have revealed that for

beta-lactams, activity against microorganisms correlates with the duration of time that the concentration of the drug remains above the MIC (time-dependent activity). For other antibiotics, antibacterial activity correlates not with the time above the MIC but the ratio of the drug exposure to the MIC (concentration-dependent or time-independent activity). This drug exposure is usually by the area under the curve (AUC) and compared to the MIC (AUC/MIC). The peak:MIC ratio has also been used to describe the activity of concentration-dependent drugs, but AUC/MIC is the more accurate parameter. **FIGURE 4-2** illustrates these pharmacokinetic/pharmacodynamic (PK/PD) parameters schematically, and Table 4-2 shows which parameter is most predictive of efficacy for antibiotic classes. The practical implications of these findings are in the design of antibiotic dosing schedules: Aminoglycosides are now frequently given as a single large dose daily to maximize their AUC/MIC, while savvy clinicians are administering beta-lactam drugs such as ceftazidime as continuous or prolonged infusions because of their time-dependent activity. As target values for these parameters that predict efficacy are found, there may be an increase in the individualization of dosing of antibiotics to achieve these target values.

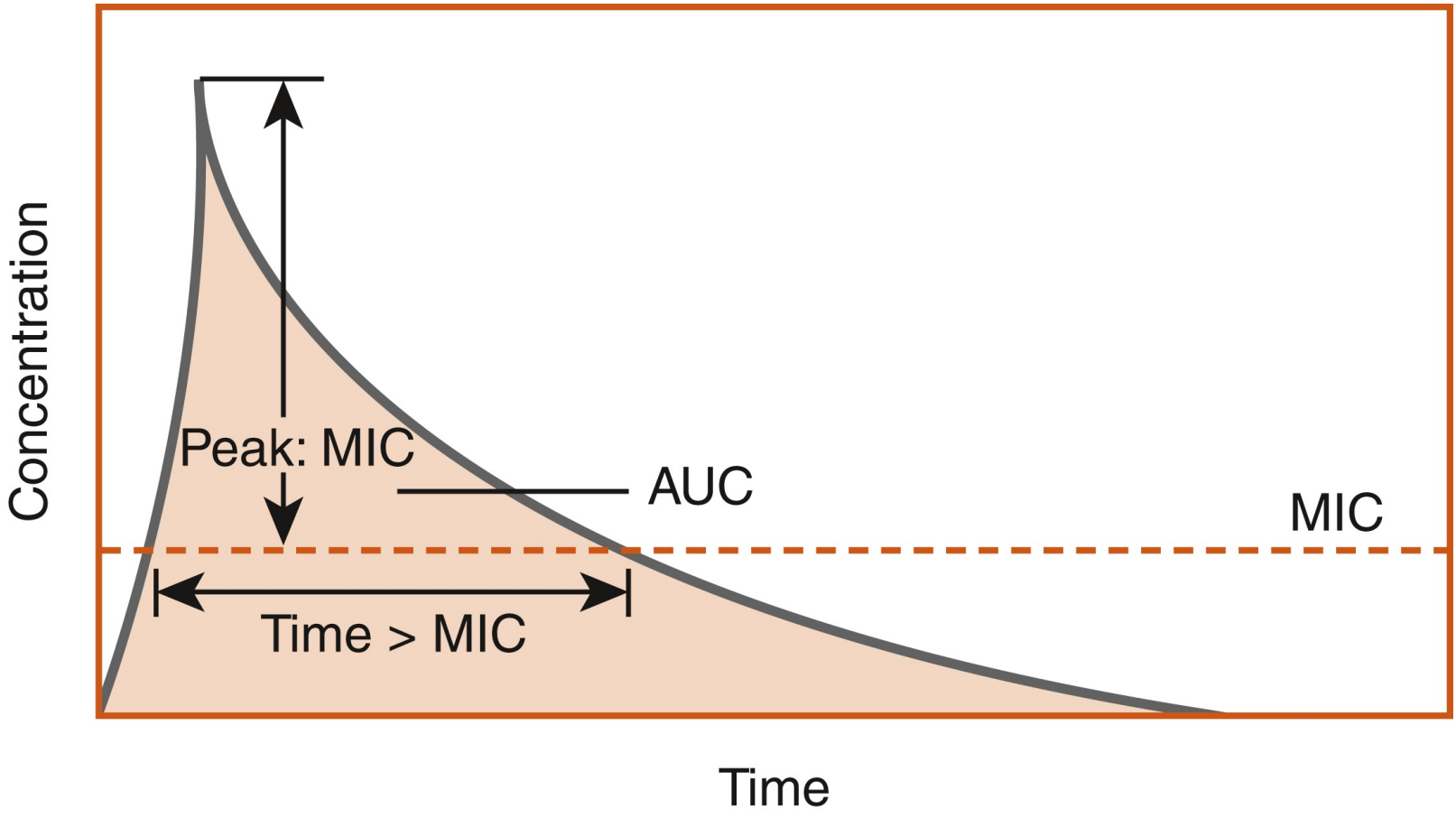

FIGURE 4-2 Pharmacokinetic/Pharmacodynamic Relationships

Description

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5

ADVERSE CONSEQUENCES OF ANTIBIOTIC USE

Although antibiotics are undoubtedly one of the most beneficial discoveries of science, their use does carry risks. They can adversely affect patients by eliciting allergic reactions, causing direct toxicity, or altering the normal bacterial flora, leading to superinfections with other organisms. Antibiotic use is the primary driving force in the development of antibiotic resistance, which can affect not only treated patients but other patients by transmission of resistant organisms. It is important to keep in mind all of these potential adverse consequences when using antibiotics.

Antibiotic Allergy

Through formation of complexes with human proteins, antibiotics can trigger immunologic reactions. These reactions may manifest immediately (such as anaphylaxis or hives) or be delayed (rashes, serum sickness, drug fever). Because of their highly reactive chemical structure and frequent use, beta-lactam drugs are the most notorious group of drugs for causing allergic reactions. It is difficult to determine how likely it is that a patient with an allergy to a particular antibiotic agent will have a similar reaction to another agent within that class. Although some (highly debated) estimates of the degree of cross-reactivity are available for beta-lactam drugs, estimates for cross-reactivity within other classes (e.g., between fluoroquinolones) are essentially nonexistent. Because labeling a patient with an allergy to a

particular antibiotic can limit *future* treatment options severely and possibly lead to the selection of inferior drugs, every effort should be made to clarify the exact nature of a reported allergy. Learning that a previous reported allergy is not accurate is termed *allergy delabeling* and can be done through careful interviewing and history taking or through skin testing.

Antibiotic Toxicities

Despite being designed to affect the physiology of microorganisms rather than humans, antibiotics can have direct toxic effects on patients. In some cases, this is an extension of their mechanism of action that can occur when selectivity for microorganisms is not perfect. For example, the hematologic adverse effects of trimethoprim stem from its inhibition of folate metabolism in humans, which is also its mechanism of antibiotic effect. In other cases, antibiotics display toxicity through unintended physiologic interactions, such as when vancomycin stimulates histamine release, leading to its characteristic vancomycin infusion reaction. Some of these toxicities may be related to the degree of drug exposure; toxicity may occur when doses are not adjusted properly for renal dysfunction and thus accumulate to a toxic level. Proper dosage adjustment can reduce the risk of dose-related toxicities.

Superinfection

The human body is colonized by a variety of bacteria and fungi. These organisms are generally considered commensals, in that they benefit from living on or in the body but do not cause harm (within their ecologic niches). Colonization with commensal organisms can be beneficial, given that they compete with and crowd out more pathogenic organisms. They may even have a role in the prevention of other human diseases and in proper immune system development. When administration of antibiotics kills off the commensal flora, pathogenic drug-resistant organisms can flourish because of the absence of competition. This is considered a superinfection (i.e., an infection on top of another infection). For example, administration of antibiotics can lead to the overgrowth of the gastrointestinal (GI) pathogen *Clostridioides difficile*, which is clinically resistant to most antibiotics. *C difficile* can cause diarrhea and life-threatening bowel inflammation. Similarly, administration of broad-spectrum antibacterial drugs can select for the overgrowth of fungi, most commonly yeasts of the genus *Candida*. Disseminated *Candida* infections carry a high risk of death. To reduce the risk of the impact of antibiotics on the commensal flora, and thus the likelihood of superinfection, antibiotics should be administered only to patients with proven or probable infections, using the most narrow-spectrum agents appropriate to the infection for the shortest effective duration.

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6
ANTIBIOTIC RESISTANCE

Though it may seem that the antibiotic era was introduced in the 1930s with the sulfonamides and penicillin, it had actually started millions of years earlier. Alexander Fleming discovered only one of the weapons of a war going on underfoot—literally, under our feet. In the soil and elsewhere, microbes are locked in life-and-death battles for dominance over each other for the limited resources they have access to. Among their weapons are antibiotics.

Causes of Antibiotic Resistance

The basic cause of antibiotic resistance is simple: antibiotic use. Some organisms, such as *Acinetobacter baumannii* or *Pseudomonas aeruginosa*, are notorious for an intrinsic ability to express multiple types of resistance. Others, such as *Klebsiella pneumoniae*, have been generally treatable for many years and are only recently becoming highly drug-resistant through acquiring new resistance elements. And some have remained highly susceptible to "old" antibiotics ever since their introduction, such as *Streptococcus pyogenes* and penicillin.

Where Does Antibiotic Resistance Come From?

In any species of bacteria, antibiotic resistance needs to have a point of origin. Resistance can emerge in the organism of interest through random mutations to the antibiotic's target or other key elements. However, it is more common that a given species of bacteria acquires the genes that encode for a mechanism of resistance from another species of bacteria that already had it

through the transfer of mobile genetic elements. Bacteria are promiscuous little organisms, and they are not picky—they often swap genes not only between their own species, but different species and even genera. There are several ways that genes are transmitted between bacteria, but the most important is by the transmission of plasmids via conjugation. Plasmids are loops of DNA that may contain multiple genes in them that encode for various processes (including antibiotic resistance), and they are highly portable. Since plasmids can contain multiple genes, they can encode for multiple types of resistance that are not related, such as resistance to cephalosporins via the production of a beta-lactamase and resistance to fluoroquinolones due to an efflux pump. With one act of gene swapping, a multiply-resistant bacterial strain is born.

Mechanisms of Antibiotic Resistance

The multiple mechanisms by which resistance occurs can be confusing, but here we are going to—wait for it—simplify it into four basic mechanisms, which are outlined in **FIGURE 6-1**.

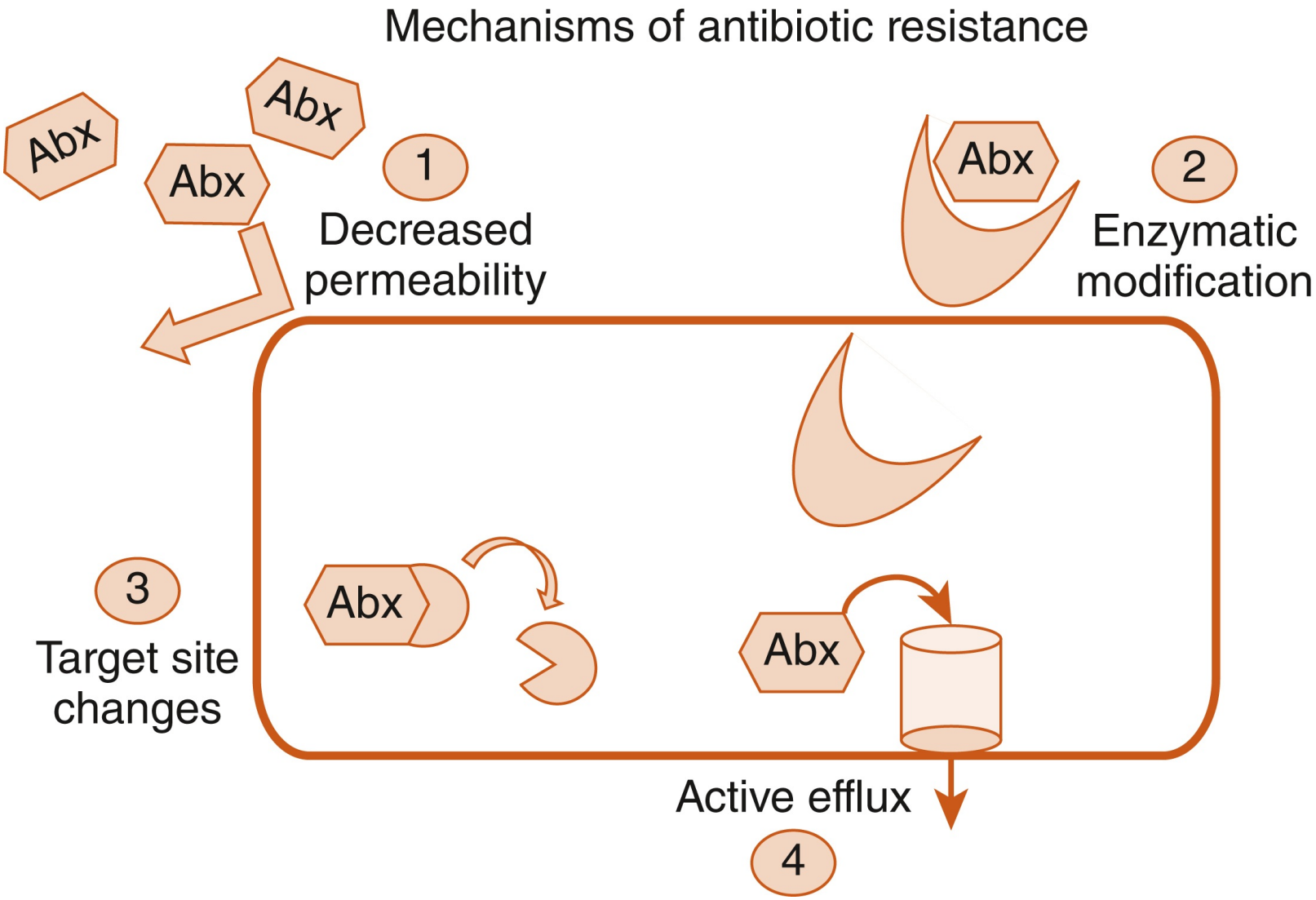

FIGURE 6-1 Mechanisms of Antibiotic Resistance

Description

Decreased permeability lowers the amount of antibiotic penetrating the bacterial cell, decreasing the intracellular concentration of the antibiotic. *Enzymatic modification* due to an enzyme produced by bacteria destroys the antibiotic before it has a chance to reach its site of

activity. *Target site changes* lead to a loss or modification of the antibiotic's site of action (e.g., a protein) such that it cannot work. *Active efflux* occurs when efflux pumps in bacteria pump out antibiotics, decreasing intracellular concentrations. Examples of how common mechanisms of resistance fall into these four broad categories are given in **TABLE 6-1**.

TABLE 6-1 Examples of Mechanisms of Antibiotic Resistance

Category	Example
Decreased permeability	Cell wall changes
	Porin channel changes or loss
	Biofilm production
Enzymatic modification	Beta-lactamases (thousands of different types!)
	Aminoglycoside-modifying enzymes
	Methylation
Target site changes	PBP 2a expression in *Staphylococcus aureus*
	PBP 2x expression in *Streptococcus pneumoniae*
	Ribosomal modification
Active efflux	Tetracycline efflux
	Fluoroquinolone efflux

Knowing the mechanism of resistance for a particular bug–drug combination is not essential in most clinical situations. Multiple mechanisms of resistance are often present and being expressed simultaneously, making it impossible to infer the mechanism of resistance just from the reported sensitivities. We have highlighted situations where it is more important throughout the antibacterial chapters in this text.

Antibiotic Pressure and Collateral Damage

Antibiotic use has consequences. Antibiotics are the only class of drug for which their use in one person affects their utility in another person, since microorganisms are transmissible. *Antibiotic pressure* is a term that reflects the fact that antibiotic-resistant strains may emerge when antibiotic-susceptible strains are killed. If a patient is infected or colonized with both resistant and susceptible strains of a bacteria, the use of an antibiotic will kill the susceptible strain and allow the resistant strain to grow. This pressure is worth the trade-off when the patient has an infection and requires treatment, but excessive pressure placed on the microorganisms in the patient can be limited by how we use antibiotics. *Collateral damage* is a term used to describe the impact of antibiotic use on microorganisms in the body beyond the targeted organism. Every dose of antibiotics affects not just the pathogen causing an infection, but potentially the billions of other bacteria in and on the body—bacteria that are just minding their business and often helping us out by preventing colonization by more aggressive bacteria. Collateral damage will occur with any antibiotic, but it can be minimized by using less-broad-spectrum antibiotics and, perhaps most importantly, minimizing the duration of use of all antibiotics when possible. One of the greatest concerns and most contentious issues in antibiotic resistance is the use of antibiotics in agriculture, which is where most antibiotics in the United States are used. The impact of this and the collateral damage that it has on the human microbiome are just beginning to be determined.

The ESKAPE Pathogens

Antibiotic resistance has been described in most bacteria that cause human infection, but some pathogens are particularly problematic. There have been several ways to describe the most serious antibiotic-resistance threats that plague mankind, but probably the most commonly utilized one is the acronym *ESKAPE* (**TABLE 6-2**).

TABLE 6-2 "ESKAPE" Pathogens and Other Resistance Threats

"ESKAPE" pathogens	*Enterococcus faecium* *S aureus* *K pneumoniae* *A baumannii* *P aeruginosa* *Enterobacter* species
Organisms classified by the CDC as an urgent health threat	*Candida auris* Carbapenem-resistant Enterobacterales Carbapenem-resistant *Acinetobacter* *C difficile* Drug-resistant *Neisseria gonorrhoeae*

These diverse organisms have in common both a high propensity for antibiotic resistance and limited options for treating their resistant phenotypes. The Centers for Disease Control and Prevention (CDC) published a report in 2013 titled "Antibiotic Resistance Threats in the United States, 2013" that details the estimated threat of resistance in the United States, available at www.cdc.gov. It estimated that 23,000 people in the United States die each year due to resistant bacterial infections, but that figure did not include the estimated 14,000 deaths per year from *Clostridioides difficile* infection.

Preventing Antibiotic Resistance: A Problem of Perspective

With all of this good news, what can we do to prevent antibiotic resistance? Convincing data show that limiting antibiotic use limits antibiotic resistance. This has been shown on many levels, from the patient to the hospital to the country level. Unfortunately, each of these levels has a different perspective. Patients want to get better and may not know that the antibiotic they are requesting is unlikely to work for a viral respiratory infection. Hospitals are concerned with both patient outcomes and costs, and diagnostic uncertainty drives much empiric antibiotic use. Many clinicians are afraid to miss a potential infection and end up using antibiotics for patients who actually do not have bacterial infections. Only the societal viewpoint is high-level enough to really look at overall antibiotic use and how it impacts antibiotic resistance.

Clinicians often think that patients come to them seeking antibiotics, but data show that they are often seeking validation of their concerns and a plan. Patients with likely viral infections of the respiratory tract can be given plans that focus on symptom management and defer antibiotic use until symptoms have a chance to improve (or not). Patients should also be educated on viral illnesses; polling of the authors' classes shows that even pharmacy students don't know that the average duration of cough from a viral infection is 2–3 weeks!

Guidelines

Decisions to use antibiotics are not made by society; they are made on a patient basis. It falls upon all of us to make therapy decisions with antibiotic resistance in mind. The following sections provide general guidance for utilizing antibiotics.

Avoid Using Antibiotics to Treat Colonization or Contamination

A substantial percentage of all antibiotic use is directed toward patients who are not truly infected, but in whom organisms are recovered from culture. Isolation of *Staphylococcus epidermidis* from a single blood culture or *Candida* species from a urinary culture in a catheterized patient are common situations in which patients should be scrutinized to determine whether an infection is truly present. Diagnostic improvements need to be developed and utilized when they are available. A simple test that could distinguish a cold from a bacterial infection could save society billions in avoided antibiotic use, resistance, and adverse effects.

Use the Most Narrow-Spectrum Agent Appropriate for the Patient's Infection

Broader-spectrum agents multiply the number of bacteria affected by the drug, increasing the chances both for development of resistance and superinfection. "Broader" and "newer" are not synonymous with "better." For example, good old penicillin kills susceptible organisms more rapidly than almost any drug on the market. The treating clinician's goal always should be definitive, narrow-spectrum therapy.

Use the Proper Dose

Bacteria that are exposed to low concentrations of antibiotics are more likely to become resistant than those exposed to effective doses—Alexander Fleming noted this 80 years ago. After all, dead organisms don't mutate! Further research in pharmacodynamics should make it easier to determine the proper dose for each patient and thus to reduce the likelihood that resistance will develop.

Use the Shortest Effective Duration of Therapy

"Take all of your antibiotics, even after you feel better." Who among us hasn't heard or said this phrase? People often think it is to prevent antibiotic resistance from emerging, but evidence to support that is largely nonexistent. Unfortunately, duration of therapy is one of the least-studied areas of infectious diseases. Examination of standard treatment durations says much more about how humans think than about how antibiotics and bacteria truly interact. Durations are typically 5, 7, 10, or 14 days, more in line with our decimal system, football scores, and the days in a week than with anything studied precisely. New studies are showing that shorter durations of therapy are often just as effective as prolonged courses and less likely to select for resistance (**TABLE 6-3**). As studies progress and determine additional factors that indicate when infections are sufficiently treated, it should be possible to define more accurately the length of therapy on a patient-by-patient basis. Many clinicians find that "old habits die hard," but they should remember that learning new evidence about the duration of therapy is important as it emerges.

TABLE 6-3 Example Infections Where Shortened Durations of Therapy Are as

Effective as Longer Standards

Infection	Shortened Therapy (Days)	Ye Olde Standard (Days)
Community-acquired pneumonia	5	10
Hospital-acquired pneumonia	8	15 (or 21)
Intra-abdominal infections	4	7–10
Cellulitis	5–6	10
Pyelonephritis in women	5–7	10–14
Male uncomplicated urinary tract infections	7	14
Uncomplicated gram-negative bacteremia	7	14

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PART 2

ANTIBACTERIAL DRUGS

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7

BETA-LACTAMS

INTRODUCTION TO BETA-LACTAMS

Beta-lactams, our largest category of antibiotics, can seem overwhelming. Penicillins, cephalosporins, and carbapenems are all beta-lactams. Monobactams (aztreonam) are structurally similar, but they lack one of the two rings that other beta-lactams have and have little to no cross-allergenicity with other beta-lactams. To make matters more confusing, not all beta-lactams end in *-cillin* or *-penem* or start with *ceph-*.

We believe the best approach to keeping beta-lactams straight is to group them into classes and learn the characteristics of each class. If you work in a hospital, you will likely have only one or two drugs of each class to worry about. In the outpatient setting, you will encounter many more of them. Fortunately, all beta-lactams have a few things in common:

- All beta-lactams can cause hypersensitivity reactions, ranging from mild rashes to drug fever to acute interstitial nephritis (AIN) to anaphylaxis. There is cross-reactivity between some agents (e.g., amoxicillin and cephalexin), but it is difficult to predict exactly how often that will occur. Studies on the matter differ greatly in their conclusions, though on the whole cross-reactivity seems to be much lower between different types of beta-lactams than previously thought. It seems that similarities between side chains of beta-lactams are

responsible for cross-reactivity and that the likelihood of allergic reactions can be predicted by them, but this has not yet disseminated widely into clinical practice.

- Seizures can result from very high doses of any beta-lactam, and some cause other neurologic effects. Accumulation to toxic levels can occur when the dose of a beta-lactam is not properly adjusted for a patient's renal function. Did you check your patient's renal function?
- All beta-lactams share a mechanism of action—inhibition of transpeptidases (i.e., penicillin-binding proteins) in bacterial cell walls, leading to swelling and lysis, killing the organism. Thus, giving two beta-lactams in combination for the same bacteria is generally not useful, but also not antagonistic. (The penicillin-binding protein doesn't care which drug binds to it.) There are a few exceptions to this rule, but not many.
- All beta-lactams can be destroyed by *beta-lactamases*, enzymes produced by bacteria to destroy beta-lactams. Some beta-lactams such as penicillins are easily destroyed, whereas others such as carbapenems are stable against most beta-lactamases. But nature has shown us that whenever a beta-lactam is developed, a beta-lactamase capable of hydrolyzing it inevitably emerges.
- All beta-lactams lack activity against atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Add another drug to your regimen if you are concerned about these organisms, as in cases of community-acquired pneumonia (CAP).
- All but one of the currently available beta-lactams lack activity against methicillin-resistant *Staphylococcus* (MRSA). Add vancomycin or another agent if this bacterium is suspected (but note that its epidemiology is changing). Among the available beta-lactams, only the cephalosporin ceftaroline has anti-MRSA activity. It is the exception that proves the rule.

Once you know the similarities among beta-lactams, it is easier to learn the differences among them.

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PENICILLINS

INTRODUCTION TO PENICILLINS

Penicillins are one of the largest and oldest classes of antimicrobial agents. Since the development of the natural penicillins in the 1930s, further penicillin development has been directed by the need to combat increasing antimicrobial resistance. Classes of penicillins with expanded gram-negative spectra overcome the shortfalls of natural penicillins, and they can be grouped fairly easily by spectrum of activity.

Penicillins have several things in common:

- Penicillins have very short half-lives (<2 hours) and must be dosed multiple times per day or by continuous infusion. The half-lives of most penicillins are prolonged in the presence of renal dysfunction.
- Like other beta-lactams, penicillins can cause hypersensitivity reactions. If a patient has a true IgE-mediated hypersensitivity reaction to a penicillin, other penicillins should be avoided, even if they are from different subclasses of penicillins. If the reaction is not severe, cephalosporins or carbapenems may be useful.
- Many penicillins are relatively poorly absorbed, even those available as oral formulations. This can lead to diarrhea when oral therapy is needed. Pay attention to the dosing of oral versus intravenous (IV) penicillins—often, a conversion from IV to oral therapy means there will be a substantial decrease in the amount of active drug in the body. Well-absorbed

penicillins such as amoxicillin may have dose-limiting gastrointestinal tolerability issues.

Many penicillins were developed after the natural penicillins became available. Until researchers developed beta-lactamase inhibitors, development primarily focused on *either* improved activity against staphylococci (MSSA) *or* gram-negative rods (GNRs) (**FIGURE 7-1**).

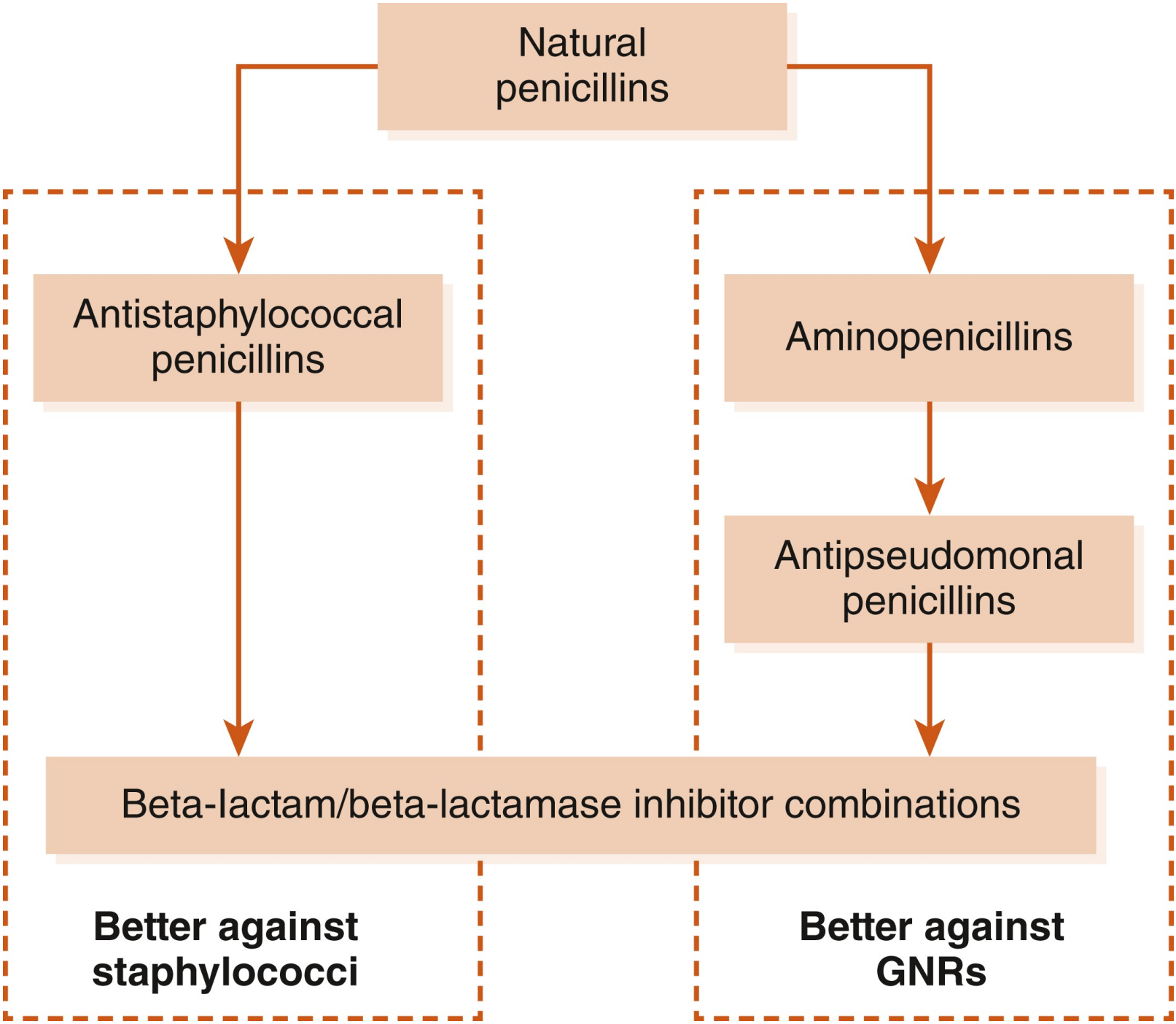

FIGURE 7-1 Penicillin Drug Development

Description

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NATURAL PENICILLINS

Agents: *penicillin G*, penicillin V

All of us have heard of the discovery of penicillin by Sir Alexander Fleming in 1929. Once penicillin was produced in medically useful quantities years later, it had a major impact on society, particularly in the treatment of wound infections. The importance of this discovery became apparent during World War II, when the Allies had access to life- and limb-saving penicillin and the Axis did not. Unfortunately, staphylococci quickly became resistant to penicillin through the production of penicillinases (beta-lactamase enzymes active against penicillins), initiating the search for new beta-lactams and leading to the confusing array of these drugs available today. The development of resistance has narrowed the spectrum of effectiveness of natural penicillins considerably over the past 60 years, such that staphylococci are almost universally resistant to them. Occasionally we still see an isolate of Staphylococcus aureus that does not produce penicillinase and is susceptible to penicillin.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: Treponema pallidum, most streptococci, including *Streptococcus pneumoniae*

Moderate: Enterococci

Poor: Almost everything else

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- Natural penicillins have a very short half-life and must be dosed frequently or given by continuous infusion. Long-acting depot formulations (procaine, benzathine) are available for intramuscular administration. It is important to know the differences among these formulations because the doses vary considerably. It is even more important not to give procaine or benzathine products intravenously, which can be fatal.
- Penicillin V is the oral form of penicillin G. Other drugs have supplanted it in most uses, but not all.
- Penicillin G remains the drug of choice for syphilis.
- Because of resistance, penicillin is a poor empiric choice for most infections. Not all textbooks and references have been updated to reflect the changes in penicillin use that have resulted from widespread resistance.
- The Clinical and Laboratory Standards Institute (CLSI) breakpoint for *S pneumoniae* to penicillin differs by both formulation and indication. The breakpoint for using oral penicillin for any indication and for using IV penicillin for central nervous system (CNS) infections is 0.06 mcg/mL, whereas the breakpoint for IV penicillin for everything else is 2 mcg/mL. These breakpoints reflect the facts that (1) systemic concentrations of oral penicillin are limited and (2) CNS penetration of IV penicillin is limited.

What They’re Good For

Syphilis, particularly neurosyphilis. During penicillin shortages, hospitals often reserve its use for this indication. Penicillin is also used in susceptible streptococcal infections such as pharyngitis or endocarditis.

Don’t Forget!

Other, more conveniently dosed narrow-spectrum beta-lactams are available for most bugs treatable with penicillin.

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ANTISTAPHYLOCOCCAL PENICILLINS

Agents: *nafcillin, oxacillin*, dicloxacillin, *methicillin*

It did not take long for *Staphylococcus* species to become resistant to penicillin. Within a few years of penicillin becoming widely available, staphylococcal strains began to produce beta-lactamases, rendering penicillin useless in these infections. The basic structure of penicillin was modified to resist these destructive enzymes, leading to the antistaphylococcal penicillins. This modification gave these drugs activity against staphylococci that produce penicillinases, but it did not add to the poor gram-negative activity of the natural penicillins.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: MSSA, streptococci

Poor: GNRs, enterococci, anaerobes, MRSA

Adverse Effects

Similar to those of other beta-lactams, with a possibly higher incidence of AIN.

IMPORTANT FACTS

- Antistaphylococcal penicillins have a short half-life and must be dosed frequently. This presents a problem because they cause phlebitis. Does your patient have phlebitis? Try a first-generation cephalosporin instead. In general, they are easier to administer, better tolerated, and a good choice for most patients.
- Most antistaphylococcal penicillins are eliminated from the body in large part by the liver and do not need to be adjusted in cases of renal dysfunction.
- These drugs are interchangeable therapeutically. Therefore, S aureus that is susceptible to methicillin (which is no longer used) is susceptible to oxacillin, nafcillin, and the rest. That is, MSSA = OSSA = NSSA, etc. The “standard tests” are usually done with either oxacillin or cefoxitin, not methicillin.

What They’re Good For

Infections caused by MSSA, such as endocarditis, bloodstream infections, and skin and soft-tissue infections.

Don’t Forget!

Beta-lactams kill staphylococci more quickly than vancomycin, so patients with MSSA infections who lack serious beta-lactam allergies should be switched to beta-lactams, such as antistaphylococcal penicillins or first-generation cephalosporins. This has been shown to be an important difference in serious infections.

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AMINOPENICILLINS

Agents: amoxicillin, *ampicillin*

Though the antistaphylococcal penicillins improve on the gram-positive coverage of natural penicillins, they do not add to their gram-negative coverage. Aminopenicillins are more water-soluble and pass through porin channels in the cell wall of some gram-negative organisms. However, they are susceptible to beta-lactamases, and resistance to them is common. Aminopenicillins are rarely active against staphylococci, because these almost always produce penicillinases. These drugs also do not have useful activity against *Pseudomonas aeruginosa*.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: Streptococci, enterococci

Moderate: Enteric GNRs, *Haemophilus*

Poor: Staphylococci, anaerobes, *Pseudomonas*

Adverse Effects

Similar to those of other beta-lactams. Aminopenicillins have a high incidence of diarrhea when

given orally.

IMPORTANT FACTS

- Though ampicillin can be given orally, amoxicillin is a better choice. It is more bioavailable, better tolerated, and administered less frequently. Use ampicillin for IV therapy and amoxicillin for oral therapy. Europeans disagree; they use amoxicillin intravenously also.
- Ampicillin is a drug of choice for susceptible enterococci. *Enterococcus faecalis* is almost always susceptible; *Enterococcus faecium* is usually resistant.
- These drugs are often listed as alternative regimens for urinary tract infections (UTIs) in pregnant women because they are pregnancy category B and eliminated renally. However, resistance in *Escherichia coli* to them is very high, and susceptibility testing should be performed. Always perform follow-up cultures in pregnant women with UTIs since even asymptomatic bacteriuria is dangerous for them.

What They’re Good For

Infections caused by susceptible GNRs, enterococci, and streptococci. Amoxicillin is frequently prescribed for infections of the upper respiratory tract, including streptococcal pharyngitis (strep throat) and otitis media (ear infection).

Don’t Forget!

Beta-lactamases have greatly limited the utility of these agents for enteric gram-negative infections, but not for streptococci or *E faecalis*. But, if you have culture results and a GNR is susceptible to an aminopenicillin alone, why give it with a beta-lactamase inhibitor and destroy more normal flora?

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PENICILLIN/BETA-LACTAMASE INHIBITOR COMBINATIONS

Agents: *ampicillin/sulbactam*, amoxicillin/clavulanate, *piperacillin/tazobactam*

Aminopenicillins have activity against GNRs that is limited by beta-lactamases. Piperacillin is like an "amped up" aminopenicillin that is active against *P aeruginosa* also. (We call it an *antipseudomonal penicillin*.) Together, these drugs have good intrinsic activity against GNRs, but they remain just as susceptible to beta-lactamases as penicillin G. This means that they are not useful against the vast majority of staphylococci, many GNRs, or anaerobes, because these organisms have learned to produce beta-lactamase. In other words, it seemed we learned either how to make a penicillin resistant to beta-lactamase or how to make it more active against GNRs, but not both. The beta-lactamase inhibitors sulbactam, clavulanate, and tazobactam counter beta-lactamases; these drugs mimic the structure of beta-lactams but have little antimicrobial activity on their own. They bind to beta-lactamases irreversibly, preventing the beta-lactamase from destroying any beta-lactams that are coadministered and enabling the therapeutic beta-lactam to be effective.

When considering the activity of a beta-lactamase inhibitor combination, remember that the beta-lactamase inhibitor only frees up the beta-lactam to kill the organism—it doesn't enhance the activity. Therefore, the combination products are active only against the bacteria that the beta-lactam in the combination has intrinsic activity against in the absence of beta-lactamase production. For example, ampicillin/sulbactam is active against beta-lactamase producing *E coli* because ampicillin alone is active against non-beta-lactamase producing *E coli*. However, it has no useful activity against *P aeruginosa*, because ampicillin lacks activity against this organism. In contrast, piperacillin/tazobactam is active against *P aeruginosa* because piperacillin itself is

active. Though these drugs have very broad spectra of activity, there are differences among the agents. Keep in mind the rule that beta-lactamase inhibitors restore activity, not add to it, to set them straight.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death. These beta-lactamase inhibitors structurally resemble beta-lactams and bind to many beta-lactamases, rendering them unable to inactivate the coadministered beta-lactam.

Spectrum

Good: MSSA, streptococci, enterococci, many anaerobes, enteric GNRs, *P aeruginosa* (only piperacillin/tazobactam)

Moderate: GNRs with advanced beta-lactamases

Poor: MRSA

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- Unlike the other members of this class, amoxicillin/clavulanate is available orally. Various doses are available, but higher doses are associated with more diarrhea. The most common dose of clavulanate in oral dosage forms is 125 mg, although variability can be seen with pediatric and long-acting formulations.
- The beta-lactamase inhibitors packaged in these combinations are not active against all beta-lactamases. New beta-lactamases with the ability to destroy many types of beta-lactams are continually being discovered and are becoming more prevalent.
- An area of debate within the ID community is whether penicillin/beta-lactamase inhibitor combinations can be used against organisms that produce *extended-spectrum beta-lactamases* (ESBLs). A landmark clinical trial called *MERINO* showed that, at least for bacteremia, a carbapenem worked better than piperacillin/tazobactam for organisms producing ESBLs. It is possible that penicillin/beta-lactamases inhibitors may still be used for less severe infections, such as UTIs.
- Sulbactam has useful activity against *Acinetobacter baumannii*, a highly drug-resistant GNR that causes nosocomial infections. However, it is not available on its own. For this reason, high doses of ampicillin/sulbactam are used in the treatment of infections caused

by this organism.

What They're Good For

Empiric therapy of nosocomial infections, particularly nosocomial pneumonia (piperacillin/tazobactam). Because they have activity against aerobes and anaerobes, they are a good empiric choice for mixed infections, such as intra-abdominal infections, diabetic ulcers, and aspiration pneumonia. Amoxicillin/clavulanate is used for upper and lower respiratory tract infections when beta-lactamase–producing organisms are found or suspected. It can also be useful for UTIs when resistance to other drugs is seen, but it should not be given for a short 3-day course, as with fluoroquinolones or TMP/SMX.

Don't Forget!

Narrow your coverage once culture results return. These are good choices of empiric therapy but poor choices of definitive therapy if alternatives are available. Be sure you know which drugs are antipseudomonal and which are not—this is a major difference among these agents that drives their use. For example, ampicillin/sulbactam is a poor choice for nosocomial pneumonia, and piperacillin/tazobactam is overkill for CAP.

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CEPHALOSPORINS

INTRODUCTION TO CEPHALOSPORINS

The cephalosporins are probably the most confusing group of antibiotics. For convenience, they have been grouped into “generations” that largely correlate with their spectrum of activity, with some notable exceptions. Although there are many different individual agents, the good news is that most hospitals use only a few of them; so, in practice, learning your institution’s cephalosporin of choice is easy. (Outpatient practice is a different story.) In general, it is best to learn the characteristics of each generation and then learn the quirks about the individual agents. **FIGURE 7-2** shows the general types of antimicrobial activity of the cephalosporin generations.

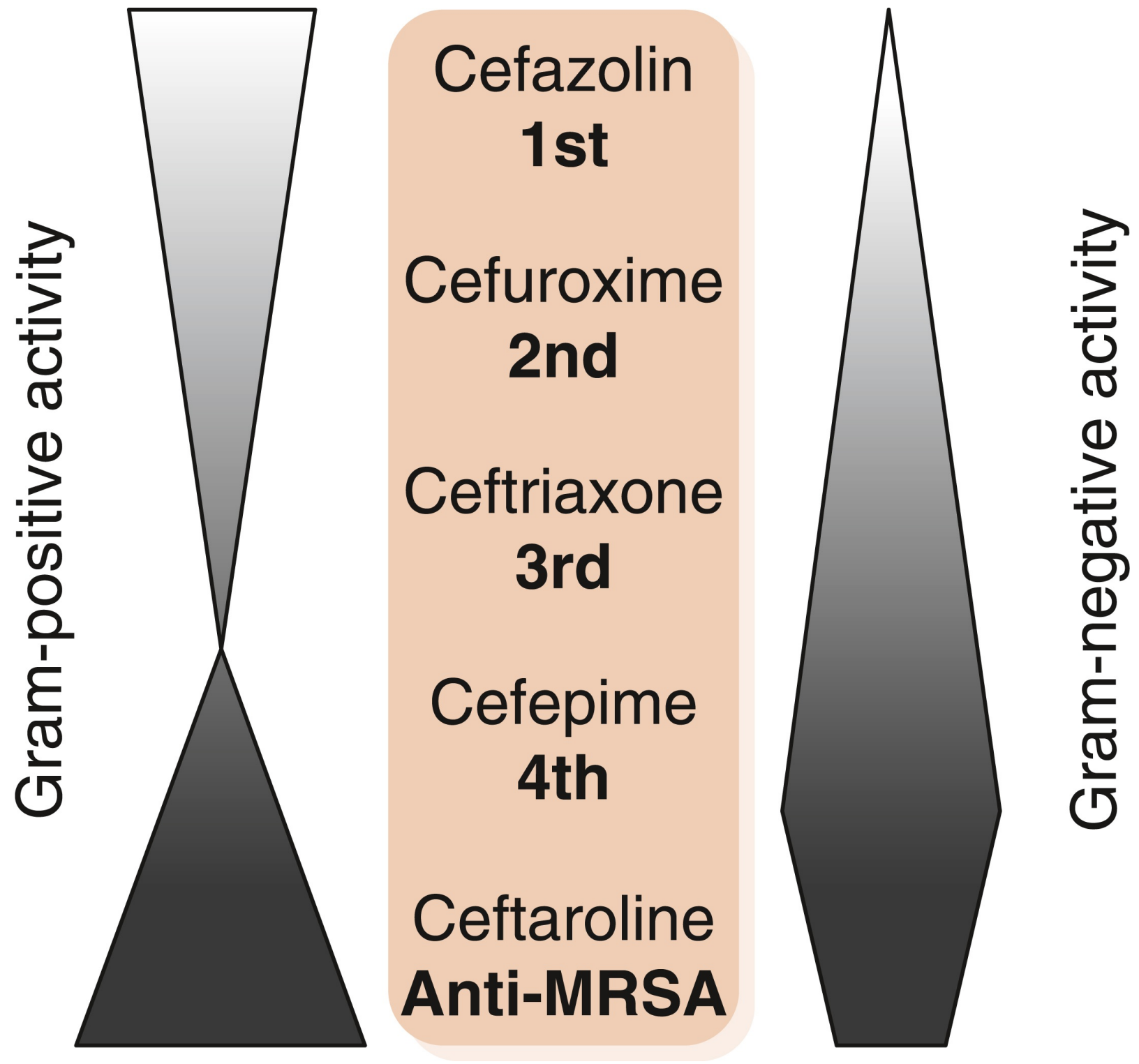

FIGURE 7-2 Cephalosporin Activity by Generation

Description

Cephalosporins have several elements in common:

- A historical belief exists that, as a class, cephalosporins have some cross-allergenicity with penicillins, though there are significant differences among generations and even agents within a generation. Estimates about the likelihood of cross-reactivity between penicillin and cephalosporin allergies differ. A reasonable estimate is less than 3%, though some publications support even lower numbers, particularly for later-generation agents. However, using any cephalosporin in a patient with a penicillin allergy is a matter of balancing risks

and benefits. Assess the validity of the patient's allergy through an interview and consider the level of risk associated with cephalosporin administration along with the benefits of using a beta-lactam compared to an alternative. Be skeptical of nausea, but be sure to take hives and any signs of anaphylaxis very seriously! Use alternative classes of antibiotics when necessary. As mentioned earlier, evidence suggests that similar side chains are the reason for cross-reactivity, but this message isn't fully "out there" yet.

- The cephalosporins are generally more resistant to beta-lactamases than penicillins are. Beta-lactamases that are active against penicillins but inactive against cephalosporins are called *penicillinases*. Beta-lactamases that inactivate cephalosporins (*cephalosporinases*) such as ESBLs also exist and are increasing in prevalence.

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FIRST-GENERATION CEPHALOSPORINS

Agents: *cefazolin*, cephalexin, cefadroxil

First-generation cephalosporins are the most commonly used class of antibiotics in the hospital. Why? They are used immediately prior to surgery to prevent surgical site infections. Their spectrum of activity, inexpensive cost, and low incidence of adverse effects make them ideal for this purpose. For the same reasons, they are useful in treating skin and skin structure infections as well.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: MSSA, streptococci

Moderate: Some enteric GNRs

Poor: Enterococci, anaerobes, MRSA, *Pseudomonas*

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- First-generation cephalosporins are good alternatives to antistaphylococcal penicillins. They cause less phlebitis and renal dysfunction and are infused less frequently.
- Cephalexin and cefadroxil are available orally; the others are parenteral. Cefadroxil is dosed twice-daily and is more convenient than the 3–4 times daily dose of cephalexin most commonly used.
- Cephalexin and cefadroxil have similar-to-identical side chains with ampicillin and amoxicillin, and cross-reactivity between these agents is high. The second generation cephalosporins cefaclor and cefprozil also share these side chains. Cefazolin does not share a side chain with any other beta-lactam, and cross-reactivity is likely very low with this drug.

What They’re Good For

Skin and skin structure infections, surgical prophylaxis, staphylococcal bloodstream infections, osteomyelitis, and endocarditis (MSSA).

Don’t Forget!

Surgical prophylaxis is the most common indication for first-generation cephalosporins in the hospital. Be sure to limit the duration of therapy for this use; administering more than one dose of antibiotics should be the exception, and giving more than 24 hours of antibiotics is rarely justified. Such use does not lower infection rates, but it can select for more resistant organisms later in the hospital stay.

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SECOND-GENERATION CEPHALOSPORINS

Agents: *cefuroxime, cefoxitin, cefotetan, cefprozil, cefaclor*

Compared with first-generation cephalosporins, second-generation agents have better gram-negative activity and somewhat weaker gram-positive activity, though they are still used for these organisms. They are more stable against gram-negative beta-lactamases and are particularly active against *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Perhaps in part because they are not as active against gram-negative organisms as third-generation agents, there are many second-generation cephalosporins that are no longer used.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: Some enteric GNRs, *Haemophilus*, Neisseria

Moderate: Streptococci, staphylococci, anaerobes (only cefotetan, cefoxitin)

Poor: Enterococci, MRSA, *Pseudomonas*

Adverse Effects

Similar to those of other beta-lactams. Cefotetan has an N-methylthiotetrazole (MTT) side

chain, which is associated with inhibition of vitamin K production and prolonged bleeding. It can also cause a disulfiram-like reaction when coadministered with ethanol. (Admittedly, *most* people in the hospital do not have access to alcoholic beverages while being treated for infections.)

IMPORTANT FACTS

- Cefoxitin and cefotetan are cephamycins. They are grouped with the second-generation cephalosporins because they have similar activity, with one important exception: anaerobes. Cephamycins have activity against many anaerobes in the gastrointestinal (GI) tract, and cefoxitin and cefotetan are often used for surgical prophylaxis in abdominal surgery.
- Cefaclor and cefprozil have similar side chains with amoxicillin, ampicillin, cephalexin, and cefadroxil, and the likelihood of cross-reactivity in people allergic to any one of these six drugs is very high. Cefuroxime is not similar to any of these drugs but does share a side chain with cefoxitin.
- Second-generation cephalosporins are “tweeners.” They have their uses but are often passed over for other choices that fit the role better.

What They’re Good For

Upper respiratory tract infections, CAP, gonorrhea, surgical prophylaxis (cefotetan, cefoxitin, cefuroxime).

Don’t Forget!

The cephamycins have good intrinsic anaerobic activity, but resistance to them is increasing in *Bacteroides fragilis* group infections. When using cephamycins for surgical prophylaxis, limit the duration of antibiotic exposure after surgery. If an infection does develop, use alternative agents such as beta-lactamase inhibitor combinations or another gram-negative agent with metronidazole.

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THIRD-GENERATION CEPHALOSPORINS

Agents: *ceftriaxone, cefotaxime, ceftazidime*, cefdinir, cefpodoxime, cefixime

Third-generation cephalosporins have greater gram-negative activity than the first- and second-generation drugs. Most of them also have good streptococcal activity but generally lesser staphylococcal activity than previous generations of cephalosporins. These are broad-spectrum agents that have many different uses.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: Streptococci (except ceftazidime, which is poor), enteric GNRs, *Pseudomonas* (ceftazidime only)

Moderate: MSSA (except ceftazidime, which is poor)

Poor: Enterococci, *Pseudomonas* (except ceftazidime, which is good), anaerobes, MRSA

Adverse Effects

Similar to those of other beta-lactams. Third-generation cephalosporins have been shown to be one of the classes of antibiotics with the strongest association with *Clostridioides difficile* infection. Cefpodoxime has the MTT side chain, which can inhibit vitamin K production. (See the section on second-generation cephalosporins for details.)

IMPORTANT FACTS

- Ceftazidime is the exception to the spectrum of activity rule for third-generation agents. Unlike the others, it is antipseudomonal and lacks clinically useful activity against gram-positive organisms.
- Ceftriaxone, cefotaxime, and ceftazidime cross the blood–brain barrier effectively and are useful for the treatment of CNS infections. However, their differences in activity lead clinicians to use them for different types of infections. Ceftazidime is a poor choice for community-acquired meningitis, in which *S pneumoniae* predominates.
- Third-generation cephalosporins are notorious for selective for resistance among GNRs. Though they can be useful in nosocomial infections, too much broad-spectrum utilization can result in harder-to-treat organisms.
- A one-time dose of ceftriaxone 125 mg intramuscular (IM) has been a drug-of-choice for gonorrhea for many years, but the dose was increased to 250 and then to 500 mg IM due to increasing resistance. If coinfection with chlamydia cannot be excluded, patients should also receive empiric therapy for chlamydia with doxycycline 100 mg twice daily for a week.
- Ceftriaxone has the characteristic of having dual modes of elimination via both renal and biliary excretion. It does not need to be adjusted for renal dysfunction, but it does effectively treat UTIs.
- Ceftriaxone has two problems that make its use in neonates problematic: It interacts with calcium-containing medications to form crystals that can precipitate in the lungs and kidneys, which has led to fatalities, and it can lead to biliary sludging with resultant hyperbilirubinemia. Avoid ceftriaxone for neonates—cefotaxime is a safer drug for these young patients.
- Last ceftriaxone fact: It is not an ideal choice for MSSA infections. If it is used (which is debated—the authors generally avoid it), it should be given in higher doses of 2–4 g a day for MSSA infections, particularly invasive infections. Less activity against this organism means higher doses are recommended.

What They’re Good For

Lower respiratory tract infections, pyelonephritis, nosocomial infections (ceftazidime), Lyme

disease (ceftriaxone), meningitis, gonorrhea, skin and skin structure infections, febrile neutropenia (ceftazidime).

Don’t Forget!

Ceftriaxone is a once-daily drug for almost all indications *except* meningitis. Make sure your meningitis patients receive the full 2 g IV q12h dose and also use vancomycin and ampicillin as empiric therapy (if indicated). There are a few more indications for the high dose, but meningitis is the most important one.

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FOURTH-GENERATION CEPHALOSPORINS

Agent: *cefepime*

There is only one fourth-generation cephalosporin: cefepime. Cefepime is the broadest-spectrum cephalosporin, with activity against both gram-negative organisms, including *Pseudomonas*, and gram-positive organisms. One way to remember its spectrum is to think that cefazolin (1st) + ceftazidime (3rd) = cefepime (4th).

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: MSSA, streptococci, *Pseudomonas*, enteric GNRs

Moderate: Acinetobacter

Poor: Enterococci, anaerobes, MRSA

Adverse Effects

Generally, similar to those of other beta-lactams, but cefepime may be associated with more neurotoxicity than most other beta-lactams.

IMPORTANT FACTS

- Cefepime is a broad-spectrum agent. It is a good empiric choice for many nosocomial infections, but it is overkill for most community-acquired infections. Be sure to de-escalate therapy if possible when you treat patients empirically with cefepime.
- Currently, cefepime is one of the few drugs with a susceptibility category of “susceptible, dose-dependent” (SDD) (see Chapter 4). For organisms with minimum inhibitory concentrations (MICs) that test in this category, cefepime can be utilized but must be given in sufficiently high doses. Doses of 500 mg or 1 g twice daily won’t cut it for many infections in this category.
- Cefepime briefly had a bad reputation after a meta-analysis showed increased mortality with its use compared with other drugs. Many clinicians were skeptical, however, and a more thorough FDA analysis exonerated cefepime.
- Neurotoxicity with cefepime can occur and may manifest as nonconvulsive status epilepticus. It can occur at any dose, but dose adjustment of the drug for patients with renal dysfunction is important.

What It’s Good For

Febrile neutropenia, nosocomial pneumonia, post-neurosurgical meningitis, other nosocomial infections.

Don’t Forget!

Cefepime is used primarily for nosocomial infections. Although it is indicated for infections of the urinary tract and lower respiratory tract, it is overkill for most community-acquired sources of these infections.

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ANTI-MRSA CEPHALOSPORINS

Agent: *ceftaroline*

Ceftaroline is a cephalosporin that has unique characteristics that defy the “generational” label. It is sometimes called a “fifth generation cephalosporin,” but because the CLSI has designated it an “anti-MRSA cephalosporin,” we’re going with that since it highlights the most important characteristic of the drug. What makes this agent unique is activity against MRSA. Its structure has been engineered to bind to the penicillin-binding protein 2a of MRSA, which has low affinity for other beta-lactams. It lost some of the gram-negative potency of cefepime and has gram-negative activity similar to that of ceftriaxone. It is often used as an alternative to vancomycin or daptomycin for MRSA infections.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death. Unlike other beta-lactams, ceftaroline can bind to penicillin-binding protein 2a, a type that is expressed by MRSA. This characteristic is responsible for its anti-MRSA activity.

Spectrum

Good: MSSA, MRSA, streptococci, enteric GNRs

Moderate: E faecalis (only in combination)

Poor: P aeruginosa, E faecium, Acinetobacter, anaerobes

Adverse Effects

Similar to those of other beta-lactams, with possibly a higher incidence of neutropenia seen with prolonged administration.

IMPORTANT FACTS

- As is typical for new antimicrobials, the initial FDA-approved indications for ceftaroline were “low-hanging fruit”: skin and skin structure infections and CAP. These are indications for which a great many agents are already available, though ceftaroline outperformed ceftriaxone for treatment of CAP in two of the three studies. As clinicians have gained experience with ceftaroline, it has been used for other invasive MRSA infections, including bloodstream infections, endocarditis, meningitis, osteomyelitis, and hospital-acquired pneumonia. It is unlikely that additional large randomized controlled trials will be performed with ceftaroline.
- Ceftaroline is sometimes combined with daptomycin for the treatment of serious MRSA infections. This combination is synergistic, but clinical data with it are limited to case series and retrospective studies. It is an expensive combination, so clinicians using it may want to transition to monotherapy as patients improve.
- Ceftaroline’s activity against MRSA is unique, but remember that it also has ceftriaxone-like GNR activity. If you are treating an MRSA infection, this may not be beneficial and can lead to *Clostridioides difficile* infection or selection pressure for resistance to cephalosporins in other GNRs.

What It’s Good For

Ceftaroline is approved (in the United States) for treatment of complicated skin and soft tissue infections and CAP. There are less rigorous data for other uses.

Don’t Forget!

Some references (including us just two editions ago) are describing ceftaroline as a fifth-generation cephalosporin. If you choose to categorize it this way, just don’t forget that its gram-negative activity is less compared to the fourth generation, especially as regards *P aeruginosa*.

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SIDEROPHORE CEPHALOSPORIN

Agent: *cefiderocol*

Cefiderocol is a unique drug. It has the basic structure of a cephalosporin and works to prevent peptidoglycan cross-linking, as other beta-lactams do. But it has a side chain that complexes with iron and is recognized by bacteria as a siderophore, which bacteria actively uptake. Bacteria need iron to grow. Siderophores are substances that many bacteria secrete into their environment to complex with free iron, then actively transport across their cell walls to the interior of the cell. When cefiderocol complexes with iron, bacteria recognize it as a siderophore and actively transport the complex into the cell, where it can work to prevent cell wall synthesis. This has been called a “Trojan horse” approach.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death. Cefiderocol’s siderophore side chain allows for active uptake into bacteria, avoiding some mechanisms of resistance, such as porin changes.

Spectrum

Good: P aeruginosa, enteric GNRs including ESBL- and carbapenenase-producing organisms, *Stenotrophomonas maltophilia*

Moderate: A baumannii

Poor: Anything gram positive, anaerobes

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- Cefiderocol is an expensive antibiotic that has utility against many of the most resistant gram-negative organisms in practice, including those resistant to carbapenems. It is useful when these organisms are encountered but should not be used when they are not likely.
- Performing susceptibility testing for cefiderocol requires iron-deficient media to mimic the physiologic conditions in the body, where free iron is rare and bacteria need to work to utilize it.
- Of course, cefiderocol resistance occurs. Those bacteria never quit, so susceptibility testing still needs to be performed.

What It's Good For

Cefiderocol is approved (in the United States) for treatment of complicated UTIs and hospital-acquired pneumonia. However, it is used off-label for the treatment of many types of infections caused by resistant gram-negative infections.

Don't Forget!

Cefiderocol is active against many types of resistant GNRs, but it should be used only in patients with resistance to other antibiotics.

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CEPHALOSPORIN/BETA-LACTAMASE INHIBITOR COMBINATIONS

Agents: *ceftazidime/avibactam, ceftolozane/tazobactam*

Carbapenems, the subject of the next section, have been drugs of choice for some of our most resistant GNRs for many years, so it was no surprise when resistance to them began to emerge. Carbapenem resistance is mostly seen in three key organisms that commonly cause infection: *Klebsiella pneumoniae, P aeruginosa,* and *A baumannii*. Avibactam is one of a new generation of beta-lactamase inhibitors with a mechanism of action that is different from older agents (e.g., sulbactam) and that works against many beta-lactamases produced by Enterobacterales and *P aeruginosa*. It restores the activity of ceftazidime against many of these organisms. Ceftolozane is a third-generation cephalosporin that evades many resistance mechanisms of *P aeruginosa*, and tazobactam is given with it to protect it from some beta-lactamases. Neither of the agents have good activity against *Acinetobacter*. Note the differences in the spectrum of these agents since they dictate their uses in different situations.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death. Tazobactam is a beta-lactamase inhibitor that structurally resembles beta-lactams and binds to many beta-lactamases, rendering them unable to inactivate the coadministered beta-lactam. Avibactam does not resemble a beta-lactam, but it also binds beta-lactamases and renders them inert. It inhibits a wider variety of enzymes than tazobactam.

Spectrum

Good: Pseudomonas, enteric GNRs (ceftazidime/avibactam > ceftolozane/tazobactam)

Moderate: Some streptococci (ceftolozane/tazobactam)

Poor: Many anaerobes, MRSA, MSSA, *Acinetobacter*

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- There are some differences in the spectrum of activity between these two drugs. Both are active against most multidrug-resistant *Pseudomonas*, but only ceftazidime/avibactam is active against carbapenem-resistant Enterobacterales. This difference dictates how they are used in clinical practice.
- Both agents evade many mechanisms of resistance of *Pseudomonas*, but in different ways. Ceftolozane itself is minimally affected by many *Pseudomonas*-resistance mechanisms, including its beta-lactamase—tazobactam itself adds little for this organism. Ceftazidime/avibactam relies on avibactam to inactivate beta-lactamases produced by *Pseudomonas*. It is possible to see isolates of *Pseudomonas* that are resistant to one of these drugs and susceptible to the other.
- Unlike penicillin-based beta-lactamase inhibitor combinations like piperacillin/tazobactam, there is substantial resistance to these agents among some important gut anaerobes. They are not active enough to be relied upon for those patients. If you suspect anaerobic involvement in your patient and you are using one of these agents, add metronidazole.

What They’re Good For

- *Both*: Multidrug-resistant Pseudomonas infections, mixed aerobic/anaerobic infections, infections caused by ESBL-producing organisms, intra-abdominal infections
- *Ceftazidime/avibactam*: Carbapenem-resistant Enterobacterales infections

Don’t Forget!

Even though these are new drugs and highly active against resistant GNRs, resistance to them does occur. Ask your lab to test them for your patient’s isolate. Bacteria never give up.

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CARBAPENEMS

Agents: *imipenem/cilastatin, meropenem, ertapenem*

Carbapenems, particularly imipenem and meropenem, are our broadest-spectrum antibacterial drugs. They possess a beta-lactam ring and share the same mechanism of action of beta-lactams, but they are structurally unique and differ from both penicillins and cephalosporins. Their broad spectrum makes them both appealing and unappealing for empiric therapy, depending on the infection being treated and the risk factors of the patient for a resistant organism. Imipenem and meropenem have similar spectra of activity; ertapenem has important differences in its spectrum that must be learned.

Mechanism of Action

All beta-lactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: MSSA, streptococci, anaerobes, enteric GNRs, *Pseudomonas* (not ertapenem), ESBL-producing GNRs

Moderate: Enterococci (not ertapenem), *Acinetobacter* (not ertapenem)

Poor: MRSA, penicillin-resistant streptococci

Adverse Effects

Similar to those of other beta-lactams, but imipenem has a higher propensity to induce seizures. Minimize the risk by calculating appropriate doses for patients with renal dysfunction and avoiding imipenem use in patients with meningitis, because it can cross the blood–brain barrier more readily.

IMPORTANT FACTS

- Imipenem is metabolized in the kidney to a nephrotoxic product. Cilastatin blocks the renal dehydropeptidase that catalyzes this reaction and prevents this metabolism from occurring. It is always coadministered with imipenem for this reason, so outside of a pharmacology exam, you can forget about it. The combination is dosed in terms of imipenem content.
- Carbapenems are very broad-spectrum agents. Imipenem and meropenem are particularly broad and should not be used empirically for most community-acquired infections. They are good choices for many types of nosocomial infections, particularly in patients who have received many other classes of antibiotics during their hospital stay.
- High or non-renally adjusted imipenem doses can cause seizures, but use of any carbapenem in a patient receiving valproic acid (VPA), a common medication for epilepsy, is contraindicated. They potently induce the metabolism of VPA to low levels that can lead to breakthrough seizures.
- Although ertapenem has weaker activity than the other carbapenems for only a few organisms, this difference in activity is significant enough to change the utility of the drug (think: ***E***rtapenem is the ***E***xception). Ertapenem is a poor choice for many nosocomial infections, particularly nosocomial pneumonia in which both *Pseudomonas* and *Acinetobacter* are important pathogens. However, it is administered only once a day and thus more convenient than the other carbapenems, so it is a better choice for home-infusion therapy for susceptible infections.
- Carbapenems may rarely elicit an allergic reaction in patients with a history of penicillin allergy. Recent studies in patients with a history of anaphylaxis to penicillin have shown the risk of cross-reactivity to be very low (1% or less). However, keep in mind that even if the cross-reactivity is very low between these agents, patients with a history of allergy to *any* drug are more likely to react to another one even if they are not related.
- Carbapenemases that render these drugs inert exist and are becoming more common. In the United States they are most common in the Northeast; they are very common in some other parts of the world.

What They’re Good For

All: Mixed aerobic/anaerobic infections, infections caused by ESBL-producing organisms, intra-abdominal infections

Imipenem, meropenem: Nosocomial pneumonia, febrile neutropenia, other nosocomial infections

Don’t Forget!

Check your dosing in patients with renal dysfunction to minimize the risk of imipenem-induced seizures.

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CARBAPENEM/BETA-LACTAMASE INHIBITOR COMBINATIONS

Agents: *meropenem/vaborbactam, imipenem/cilastatin/relebactam*

The rise of carbapenemases, particularly among Enterobacterales, prompted further drug development into beta-lactamase inhibitors that work against these enzymes. Avibactam (paired with ceftazidime) was the first; vaborbactam and relebactam have since been developed and paired with existing carbapenems (meropenem and imipenem, respectively). This new class of antibiotics has subtle differences between the two agents, principally for *Pseudomonas* infections.

Mechanism of Action

Like the other beta-lactams, carbapenems inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death. Vaborbactam and relebactam are non-beta-lactam beta-lactamase inhibitors that bind to beta-lactamase enzymes, allowing the carbapenems to do their job.

Spectrum

Good: MSSA, streptococci, anaerobes, enteric GNRs, *Pseudomonas*, ESBL- and carbapenemase-producing GNRs

Moderate: Enterococci, *Acinetobacter*

Poor: MRSA, penicillin-resistant streptococci

Adverse Effects

Similar to those of other beta-lactams.

IMPORTANT FACTS

- Both of these agents are active against many carbapenemases produced by Enterobacterales, particularly the types most common in the United States. However, other enzymes have of course evolved that these inhibitors do not work against. Be sure to test all isolates for susceptibility to carbapenem/beta-lactamase inhibitor combinations if you are contemplating using them.
- The key difference in the spectrum of these drugs is for carbapenem-resistant Pseudomonas infections. Relebactam restores the activity of imipenem against many of these strains. Vaborbactam does little to improve the activity of meropenem against them.
- Even when combined with relebactam, imipenem is coformulated with cilastatin. Unlike imipenem/cilastatin, imipenem/cilastatin/relebactam is dosed in terms of the total amount of all three drugs. For example, the typical dose is 1.25 g every 6 hours; this is 500 mg of imipenem, 125 mg of cilastatin, and 500 mg of relebactam. This means that a patient receiving “imipenem/cilastatin/relebactam 1.25 g IV q6h” is receiving the same amount of imipenem as one receiving “imipenem/cilastatin 500 mg IV q6h.” Yes, it’s confusing.

What It’s Good For

Gram-negative infections, including those caused by highly resistant *Pseudomonas* (imipenem/cilastatin/relebactam) and Enterobacterales (both drugs).

Don’t Forget!

The differences between these agents are subtle, but they define their uses. Both are very broad in spectrum and are best reserved for the “toughest of the tough” GNRs.

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MONOBACTAMS

Agent: *aztreonam*

Aztreonam is the only monobactam currently available. Structurally, aztreonam contains only the four-membered ring of the basic beta-lactam structure—hence, the name monobactam. Aztreonam's quirk is that it seems to be safe to administer to patients with allergies to other beta-lactams, except patients who have a specific allergy to ceftazidime. This cross-reactivity seems to be a result of the fact that ceftazidime and aztreonam share an identical side chain. (Note that ceftolozane also shares this side chain.) Ceftazidime and aztreonam also share virtually the same spectrum of activity. It is reasonably safe to remember the utility of aztreonam by thinking of it as ceftazidime without allergic cross-reactivity with other beta-lactams.

Mechanism of Action

Like the other beta-lactams, monobactams inhibit cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.

Spectrum

Good: Pseudomonas, most GNRs

Moderate: Acinetobacter

Poor: Gram-positive organisms, *Acinetobacter*, anaerobes

Adverse Effects

Similar to those of other beta-lactams but with a low incidence of hypersensitivity.

IMPORTANT FACTS

- Aztreonam shares a mechanism of action and pharmacodynamic profile with other beta-lactams. Because it is a gram-negative drug that is often used in patients with penicillin allergies, it is often confused with aminoglycosides. It is chemically unrelated to aminoglycosides and does not share their toxicities.
- Aztreonam can be administered via inhalation to patients with cystic fibrosis to prevent exacerbations of infection.

What It's Good For

Gram-negative infections, including *Pseudomonas*, particularly in patients with a history of beta-lactam allergy.

Don't Forget!

Before using aztreonam in your patients with beta-lactam allergies, investigate whether the reaction was specifically to ceftazidime. If you cannot determine this and the reaction was serious, proceed with caution or use an alternative agent.

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8

GLYCOPEPTIDES AND SHORT-ACTING LIPOGLYCOPEPTIDES

Agents: *vancomycin, telavancin*

To date, three glycopeptides are in clinical use: vancomycin, teicoplanin, and telavancin. Teicoplanin is not available in the United States.

Vancomycin is invaluable because it has activity against most things gram-positive that have not learned to become resistant to it. Many enterococci (especially *Enterococcus faecium*) have figured this out—we call them vancomycin-resistant *Enterococcus* (VRE). A few staphylococci have learned vancomycin resistance from the enterococci, but these staphylococci are currently very rare. In general, they are vancomycin-susceptible, including methicillin-resistant strains.

Telavancin is a somewhat different agent. It is a lipoglycopeptide that was modified from vancomycin's structure. It has some unique properties that may be advantageous compared with vancomycin, such as improved activity against MRSA that is less susceptible to vancomycin, but it is used primarily for patients who do not respond to vancomycin.

Mechanism of Action

Glycopeptides bind to terminal D-ala-D-ala chains on peptidoglycan in the cell wall, preventing further elongation of peptidoglycan chains. Telavancin has a second mechanism where the drug

interferes with the cell membrane also, disrupting membrane function.

Spectrum

Good: MSSA, MRSA, streptococci, *Clostridioides difficile* (given orally)

Moderate: Enterococci

Poor: Anything gram-negative

Adverse Effects

Infusion-related reactions: A histamine-mediated reaction called *vancomycin infusion reaction* is classically associated with vancomycin. (It was formerly called *red man syndrome*, and less sophisticated texts refer to it this way.) When it occurs, the patient may feel warm, flushed, and may develop hypotension. This reaction can be prevented by slowing the infusion rate and is not a true allergy. Antihistamines can also ameliorate the reaction. Because the core structure of telavancin is essentially vancomycin, it may cause this reaction as well.

Ototoxicity: Vancomycin has historically been considered an ototoxic drug, but evidence linking it with this toxicity is unclear.

Renal: Nephrotoxicity is an adverse effect classically assigned to vancomycin. Although the historical evidence linking this with vancomycin is poor, recent studies have shown that it may be nephrotoxic in higher doses, including the higher doses that are commonly used to treat MRSA infections in the twenty-first century. The early formulation of vancomycin was brown, and clinicians trying to amuse themselves dubbed it “Mississippi mud.” The current formulation is clear and lacks those potentially toxic excipients. Telavancin has renal toxicity issues as well.

Telavancin: In addition to the preceding reactions, taste disturbances and foamy urine occur with telavancin. Telavancin should not be given to pregnant women because of problems seen in animal studies.

Dosing Issues

Intravenous vancomycin is usually monitored pharmacokinetically by obtaining serum concentration levels. Classically, trough concentrations were used to ensure that the drug was not being eliminated too quickly or slowly, with different indications having different preferred trough ranges. However, troughs have not been shown to be good predictors of either safety or efficacy, and vancomycin dosing guidance has moved towards dosing based on targeted AUC (area under the concentration–time curve) values. This has two issues. One is that calculating

AUC is more complicated than simply comparing a trough concentration to a target range. The other issue is that the targeted AUC values (400–600) may lead to *lower* trough concentrations than the goals to which clinicians are accustomed (15–20 mg/L). Education of prescribers that efficacy can be attained with lower trough concentrations if the AUC is adequate is important.

IMPORTANT FACTS

- Oral vancomycin is absorbed very poorly. Its only use is for the treatment of *C difficile*–associated disease. Also, IV vancomycin does not reach intracolonic concentrations high enough to kill *C difficile*, so oral (or rectal) is the only way to go.
- Oral vancomycin achieves gut concentrations that are sky-high, so the lowest dose is the best one for the majority of patients.
- Do not overreact if your vancomycin trough is higher than expected. Was it drawn correctly? If not, check it again.
- Although vancomycin is active against staphylococci, it does not kill MSSA as quickly as beta-lactams do. Does your patient have MSSA? Use cefazolin, oxacillin, or nafcillin instead.
- Telavancin is more rapidly bactericidal than vancomycin. This activity may be an advantage in the treatment of some infections, but clinical evidence that shows a benefit is lacking at this point. It may be useful for patients not responding to other therapies for MRSA infections.

What They’re Good For

Vancomycin is a drug of choice for MRSA infections and for empiric use when MRSA is a concern, such as for nosocomial pneumonia. It is also useful in other gram-positive infections when the patient has a severe beta-lactam allergy. Telavancin is indicated for skin and skin structure infections and hospital-acquired pneumonia. Its role is still being defined.

Don’t Forget!

Are you *sure* that vancomycin trough concentration was drawn correctly? Mistimed vancomycin levels are very common, and changing doses in response to incorrect vancomycin levels can lead to over- or underdosing!

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9
LONG-ACTING GLYCOPEPTIDES

Agents: *dalbavancin, oritavancin*

Dalbavancin and oritavancin are unique agents. Pharmacologically, they start with the base structure of a glycopeptide and add structural characteristics that slow their elimination. Both can be dosed intravenously just once for the equivalent of 2 weeks of therapy since each has a half-life of over a week.

Both drugs have strictly gram-positive activity that includes MRSA and streptococci. This begs the question of where one would use drugs like these? Right now, they are both indicated for infections of the skin and skin structure, where both *Staphylococcus* and *Streptococcus* cause most infections. There is a lot of appeal to giving patients just one dose of drug for a full course of therapy (think about adherence), but it comes with a high price. They are cheaper than a hospital admission, but ensure that patients have insurance or other means of paying for the medication before you use one.

Mechanism of Action

All glycopeptides bind to terminal D-ala-D-ala chains on peptidoglycan in the cell well, preventing further elongation of peptidoglycan chains. Lipoglycopeptides have a second mechanism where the drug interferes with the cell membrane also, disrupting membrane function.

Spectrum

Good: MSSA, MRSA, streptococci, enterococci (oritavancin)

Moderate: Enterococci (dalbavancin)

Poor: Anything gram-negative

Adverse Effects

In clinical trials, nausea, vomiting, diarrhea, and rash were the most common adverse effects with both drugs. Infusion-related reactions can occur with the Orbactiv® formulation of oritavancin if it is infused quickly, so it is given over 3 hours.

IMPORTANT FACTS

- The prolonged elimination of these drugs is a significant advantage that can enable easy outpatient options and ensure “adherence” (by forcing it upon the patient with the infusion). However, these patients still need to be monitored for both treatment success and adverse effects.
- Oritavancin interferes with assays for prothrombin time (PT) for 12 hours and activated partial thromboplastin time (aPTT) for 120 hours, which are used to monitor warfarin and heparin, respectively. These drugs should not be used in combination with oritavancin during those time periods since monitoring will be unreliable.
- Dalbavancin has different dosing depending on whether it is administered twice (1000 mg on day 1, then 500 mg a week later) or once (1500 mg). Why would one use the two-dose regimen, you ask? We don’t know, but it was studied first.
- Oritavancin comes in two formulations. Orbactiv® was developed first, and it needs to be infused over 3 hours. Kimyrsa® was more recently developed and can be given over 1 hour, which is a significant advantage when given in outpatient settings.

What They’re Good For

Skin and skin structure infections in patients whose infections are either known or highly suspected to be caused by gram-positive organisms. The paradigm for which patients are best suited for these interesting drugs is still being defined.

Don’t Forget!

Patients discharged on these drugs still need monitoring—it’s not just “set it and forget it!”

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10

FLUOROQUINOLONES

Agents: *ciprofloxacin, levofloxacin, moxifloxacin, delafloxacin*

From a spectrum of activity and pharmacokinetic standpoint, many of the fluoroquinolones are near-ideal antibiotics: They have broad-spectrum activity that includes gram-positive, gram-negative, and atypical organisms; they display excellent oral bioavailability; and they distribute widely into tissues. Unfortunately, these characteristics have led to overprescribing and the inevitable rise in resistance, despite recommendations to reserve this class. In particular, although activity against enteric gram-negative organisms (such as *Escherichia coli* and *Klebsiella*) historically has been excellent, in some geographical regions and patient populations these drugs have lost much of their activity, and they are no longer recommended in the United States as first-line drugs for uncomplicated urinary tract infections (UTIs). Moxifloxacin has increased gram-positive (mostly pneumococcal) activity at the expense of some gram-negative (mostly *Pseudomonas*) activity. Delafloxacin adds activity against MRSA.

Mechanism of Action

Fluoroquinolones inhibit DNA topoisomerases, enzymes that are involved in winding and unwinding the DNA; the action of the fluoroquinolones can lead to breaks in the DNA and death of the cell.

Spectrum: ciprofloxacin

Good: Enteric GNRs (*E coli, Proteus, Klebsiella,* etc.), *Haemophilus influenzae*

Moderate: Pseudomonas, atypicals (*Mycoplasma, Chlamydia, Legionella*)

Poor: Staphylococci, *Streptococcus pneumoniae*, anaerobes, enterococci, *Acinetobacter baumannii*

Spectrum: levofloxacin/moxifloxacin

Good: Enteric gram negatives, ***S pneumoniae,*** atypicals, *H influenzae*

Moderate: Pseudomonas (*levofloxacin only*), MSSA, anaerobes (moxifloxacin)

Poor: Anaerobes (*levofloxacin*), enterococci, *A baumannii*

Spectrum: delafloxacin

Good: Enteric gram negatives, MRSA, MSSA, atypicals, *H influenzae*

Moderate: Pseudomonas, anaerobes, enterococci

Poor: A baumannii

Adverse Effects

Nervous system: Fluoroquinolones can cause central nervous system (CNS) adverse reactions, including dizziness, confusion, and hallucinations. Elderly patients are particularly susceptible to these. Younger patients may develop insomnia. Peripheral neuropathy can also occur.

Cardiovascular: Prolongation of the QT interval can be observed, but arrhythmias usually occur only in patients with other risk factors (underlying arrhythmia, concomitant proarrhythmic drug, excessive dose).

Musculoskeletal: Arthralgias (uncommonly) and Achilles tendon rupture (very rarely) may occur. Tendon rupture is more common in the elderly, patients with renal dysfunction, and those taking corticosteroids. Tendonitis usually precedes rupture, so complaints of tendon pain should be taken seriously. Less commonly, exacerbations of myasthenia gravis may occur. Vigorous exercise should be avoided during fluoroquinolone therapy, particularly in patients receiving corticosteroids. They can also exacerbate muscle weakness in patients with myasthenia gravis.

Dermatologic: Photosensitivity is often seen. Patients should avoid the sun or use sunscreen while taking fluoroquinolones.

Developmental: Because of toxicities seen in juvenile beagle dogs, fluoroquinolones are

typically avoided in pregnant women and children, although experience with use in children suggests they may be safely used if compelling indications exist.

IMPORTANT FACTS

- While ciprofloxacin and levofloxacin have activity against *Pseudomonas*, minimum inhibitory concentrations (MICs) are typically higher than with other susceptible organisms (e.g., *E coli*). Thus, when using these drugs to treat documented or possible *Pseudomonas* infections, give them at higher, antipseudomonal doses: 400 mg IV q8h or 750 mg po q12h for ciprofloxacin; 750 mg IV/po daily for levofloxacin. Delafloxacin has only one dose: 300 mg IV twice daily IV or 450 mg po twice daily.
- Bioavailability of all fluoroquinolones is high, ranging from 58 to 100%. For levofloxacin and moxifloxacin, oral dose = IV dose. Ciprofloxacin and delafloxacin are given at higher oral doses than IV to overcome moderately lower bioavailability.
- Levofloxacin, ciprofloxacin, and delafloxacin are the *only* drugs that are well-absorbed and active against *Pseudomonas*, but resistance to them is unfortunately common for this pathogen. Susceptibility testing is a must.
- Fluoroquinolones chelate cations, and their oral bioavailability is *significantly decreased* when administered with calcium, iron, antacids, milk, or multivitamins. Separate these agents by at least 2 hours or have your patient take a week off of the supplements, if possible. Administration with tube feedings is also problematic. This problem is unique to the oral formulations—IV forms avoid it.
- Most fluoroquinolones are cleared renally and require dose reduction in renal dysfunction. **Moxifloxacin is the exception**; because it is not excreted into the urine, it is also not approved for treatment of UTIs. Delafloxacin is excreted into the urine in large part, but it has not been approved to treat UTIs.
- The FDA mandates a boxed warning to all fluoroquinolone package inserts regarding the possibility of tendon rupture, tendinitis, peripheral neuropathy, central nervous system effects (seizures, psychiatric effects), and exacerbations of myasthenia gravis. These effects are all rare but serious.
- Important note: In 2016, the FDA required the addition of a warning for all systemic fluoroquinolones that their risks outweigh their benefits for most cases of sinusitis, bronchitis, and uncomplicated UTIs unless other options are not available. This is due to the possibility of rare but serious adverse effects, including those listed previously.

What They're Good For

Not everything, despite the temptation. Remember: The longer you want to be able to use these drugs, the more restraint should be exercised now. Indications for the fluoroquinolones are listed in **TABLE 10-1**.

TABLE 10-1 Indications for Fluoroquinolones

Indication	Ciprofloxacin	Levofloxacin	Moxifloxacin	Delafloxacin
CAP, sinusitis, AECB	–	+	+	+
UTI	+	+	–	?
Intra-abdominal infection	+	+	+	?
Systemic gram-negative infections	+	+	+	?
Skin/soft tissue infection	–	+	+	+
Pseudomonas infections	+	+	–	?
Treatment/ prophylaxis in bioterrorism scenarios (active vs. anthrax, plague, tularemia)	+	+	?	–

+ = approved/studied/makes sense for this indication. ? = should work, no clinical data. – = suboptimal.

Description

Don't Forget!

When using the oral forms of fluoroquinolones, be especially careful to avoid coadministering with chelating agents (calcium, magnesium, aluminum, etc.). Ask your patients if they use these, since these are available over the counter.

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AMINOGLYCOSIDES

Agents: *gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin*

The aminoglycosides as a class dispel the notion that antibiotics are nontoxic. These drugs have a narrow therapeutic window, and improper dosing carries the risk of inflicting significant toxicity (primarily nephro- and ototoxicity) on your patients. Because of this, there has been a reduction in their use as primary therapy for most infections. That being said, aminoglycosides retain activity against many problem pathogens (such as *Pseudomonas* and *Acinetobacter*) that have developed resistance to the more benign drug classes. They also synergize with the cell-wall active drugs (beta-lactams and glycopeptides) to improve the efficiency of bacterial killing. Gentamicin and tobramycin are the most widely used drugs; amikacin is generally reserved for pathogens resistant to the first two; and streptomycin has limited uses: *Enterococcus*, tuberculosis (TB), and plague. Plazomicin is the newest and was developed to have improved activity against resistant Enterobacterales. Neomycin is an aminoglycoside that is used topically.

Mechanism of Action

Aminoglycosides bind to the bacterial ribosome (the 30S subunit, if you must know), causing misreading of the genetic code, leading to incorrect protein formation and interruption of protein synthesis.

Spectrum: gentamicin/tobramycin/amikacin

Good: Gram negatives (*Escherichia coli, Klebsiella, Pseudomonas,* most others), *Mycobacteria* (*tuberculosis* and its cousins—amikacin and streptomycin only)

Moderate: In combination with a beta-lactam or glycopeptide: staphylococci (including MRSA), viridans streptococci, enterococci (gentamicin and streptomycin are best); *Acinetobacter*

Poor: Atypicals, anaerobes, gram-positive organisms (as monotherapy)

Adverse Effects

Nephrotoxicity: Oliguric acute renal failure, preceded by a rising serum creatinine, is a dose-related adverse effect of aminoglycosides. Risk can be reduced by correct dosing (including the use of extended-interval dosing), as well as avoidance of coadministration of other nephrotoxins (cyclosporine, cisplatin, foscarnet, etc.).

Ototoxicity: Aminoglycosides cause dose-related cochlear and vestibular toxicity. For patients anticipated to receive long-term (≥ 2 weeks) course of aminoglycosides, baseline and follow-up audiology are necessary. It is important to monitor patients closely for any hearing loss or balance problems, because these are not reversible and can significantly affect quality of life. They are also difficult to detect in bedridden patients.

Neurologic: Neuromuscular blockade can occur when aminoglycosides are given, particularly in high doses to patients who are receiving therapeutic paralysis.

IMPORTANT FACTS

- Once-daily or extended-interval aminoglycoside dosing leverages the concentration-dependent killing of the drugs to create an equally effective, more convenient, and possibly safer dosing regimen. However, there are many populations in which once-daily dosing has had less study, including the pregnant, the critically ill, those with significant renal dysfunction, and the morbidly obese. Use this dosing method with caution, if at all, in these populations. Aminoglycosides should be avoided if possible in pregnant women anyway due to concern for fetal adverse effects.
- Aminoglycoside serum levels can help guide appropriate dosing and reduce the risk of toxicity, but they must be drawn correctly to have meaningful interpretations. For traditional dosing methods, a peak level should be drawn half an hour after the end of the infusion, while trough levels should be drawn within 30 minutes of the next dose. For once-daily

dosing there are a number of potential monitoring points, based on published nomograms.

- Aminoglycosides achieve relatively poor concentrations in many tissues, including the lungs and central nervous system. This makes them less than optimal as monotherapy for many severe infections. It also means that a dose should be based on the patient's ideal or adjusted body weight, rather than his or her total body weight. Given the high prevalence of morbid obesity, serious overdosing of patients can occur if the patient's total body weight is used.
- While most of these drugs have been around for many years, plazomicin was approved in 2018. It was developed to be active against multidrug-resistant Enterobacterales, including strains resistant to carbapenems.
- There are minor differences between the aminoglycosides in their activity against specific organisms:
  - For *Pseudomonas*: amikacin > tobramycin > gentamicin > plazomicin
  - For *Klebsiella*: plazomicin > amikacin = gentamicin > tobramycin
- Some older drug references and textbooks list streptomycin as a first-line treatment for tuberculosis. Although streptomycin was the first antituberculosis drug available, it has been supplanted by safer and more effective first-line drugs. If an aminoglycoside is required for treatment of tuberculosis or other mycobacteria, amikacin is now the preferred agent.

What They're Good For

In combination with a beta-lactam agent, treatment of serious infections with documented or suspected gram-negative pathogens, including febrile neutropenia, sepsis, exacerbations of cystic fibrosis, and ventilator-associated pneumonia. Aminoglycosides, primarily gentamicin, are also used in combination with a beta-lactam or glycopeptide for treatment of serious gram-positive infections, including endocarditis, osteomyelitis, and sepsis. In combination with other antimycobacterials, aminoglycosides are used for treatment of drug-resistant infections with *Mycobacterium tuberculosis* or other mycobacteria (streptomycin and amikacin).

Don't Forget!

Most aminoglycoside toxicity is dose related, so get the dose right from the start by adjusting for renal dysfunction and using ideal or adjusted body weight. Pharmacokinetic concentrations are useful for monitoring and dosing aminoglycosides if they are drawn correctly.

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TETRACYCLINES AND MODIFIED TETRACYCLINES

Agents: doxycycline, minocycline, tetracycline, *tigecycline, eravacycline*, omadacycline

Tetracyclines were once considered broad-spectrum antibiotics, but the relentless advance of bacterial resistance and the off-patent status of the drugs reduced their use to niche indications. They are useful (but not highly studied) alternatives for the treatment of common respiratory tract infections and drugs of choice for a variety of uncommon infections. Doxycycline is preferred in most situations over tetracycline and minocycline. Tigecycline, eravacycline, and omadacycline are modified tetracyclines that evade most tetracycline resistance mechanisms and have a “restored” broad spectrum of activity. Are the tetracyclines “back"? Time will tell.

Mechanism of Action

Tetracyclines bind to the bacterial ribosome at the 30S subunit, preventing the docking of transfer RNA carrying new amino acids for addition to the elongating protein chain.

Spectrum: tetracycline/doxycycline/minocycline

Good: Atypicals, rickettsia, spirochetes (e.g., *Borrelia burgdorferi, Helicobacter pylori*), *Plasmodium* species (malaria)

Moderate: Staphylococci (including MRSA), *Strepto-coccus pneumoniae*

Poor: Most GNRs, anaerobes, enterococci, *Streptococcus agalactiae, Streptococcus pyogenes*

Spectrum: tigecycline, eravacycline, omadacycline

Good: Atypicals, enterococci (including VRE), staphylococci (including MRSA), *S pneumoniae, S agalactiae, S pyogenes*

Acceptable: Most GNRs, anaerobes

Poor: Pseudomonas, Proteus, Providencia (see a *p-p-p*attern?)

Adverse Effects

Gastrointestinal: Tetracyclines can cause esophageal irritation, and patients should take the drug with water, while standing up if possible. They also cause nausea and sometimes vomiting. Tigecycline, though an IV drug, can cause severe nausea, vomiting, and diarrhea.

Dermatologic: Photosensitivity is often seen. Patients should avoid the sun or use sunscreen while taking tetracyclines. Minocycline can sometimes lead to blue coloring of tissues.

Sensory: Minocycline may cause dizziness and vertigo.

Cardiovascular: Omadacycline can lead to increases in heart rate; it does not affect the corrected QT interval.

Developmental: All tetracyclines can cause discoloration of developing teeth and are contraindicated in pregnant women and children younger than 8 years old.

IMPORTANT FACTS

- Doxycycline and minocycline bioavailability is approximately 100%. Omadacycline has ~35% bioavailability and is given at oral doses higher than the IV dose to compensate. Tigecycline and eravacycline are IV only.
- Tetracyclines chelate multivalent cations, and their oral bioavailability is *decreased significantly* when administered with calcium, iron, antacids, or multivitamins with minerals. Have patients separate these agents by at least 2 hours or take a week off from the supplements, if possible. Food decreases the absorption of tetracycline substantially, but

of minocycline and doxycycline minimally. Omadacycline is best absorbed on an empty stomach—recommendations are to administer at least two hours before and four hours after a meal.

- The majority of tetracyclines are eliminated hepatically with minimal renal elimination, making them poor choices for urinary tract infections (UTIs). Tetracycline is the exception; it is eliminated renally and should not be used in cases of renal insufficiency. (It can worsen renal dysfunction.) Its efficacy for UTIs is not well established.
- Tetracyclines have large volumes of distribution, indicating that they distribute highly into many tissues. However, their extensive distribution also leads to low bloodstream concentrations, and they are not good choices for treating primary bloodstream infections.
- An analysis performed by the FDA across all indications for tigecycline showed it to have a mortality disadvantage compared to the other antibiotics studied. This was driven largely by a study of hospital-acquired pneumonia. Although this is obviously concerning, tigecycline still may be useful because it has activity against many highly drug-resistant organisms in which there are few (or no) alternatives. Those types of infections usually do not make it into clinical studies.

What They’re Good For

Uncomplicated respiratory tract infections: acute exacerbations of chronic bronchitis, sinusitis, and community-acquired pneumonia. They are drugs of choice for many tick-borne diseases. Use as alternative drugs for skin or soft-tissue infections, syphilis, pelvic inflammatory disease (with cefoxitin). Use as an alternative to ciprofloxacin in bioterrorism scenarios. (They are active against anthrax, plague, and tularemia.) Use for malaria prophylaxis and treatment. Tigecycline and eravacycline have roles in the treatment of complicated polymicrobial infections, such as intra-abdominal infections and complicated skin and skin structure infections.

Don’t Forget!

Ask patients whether they take mineral supplements (like calcium and iron) at home. Just because supplements are not on a patient’s medication profile does not mean they do not take them. A patient who washes down a tetracycline with a calcium supplement or even a (large) glass of milk may completely negate an otherwise brilliant therapeutic plan.

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13 MACROLIDES

Agents: clarithromycin, *azithromycin*, *erythromycin*

Macrolides are among the antibiotics used most frequently in the outpatient setting because of their broad coverage of respiratory pathogens. Though their coverage is broad, it is not particularly deep, because there is high resistance to these agents (especially in *Streptococcus pneumoniae*). Although erythromycin is the class patriarch, because of its adverse effects, drug interactions, and frequent dosing, it has little use except as a GI stimulant.

Mechanism of Action

Macrolides bind to the 50S subunit of bacterial ribosomes, preventing the ribosomes from shuffling along and adding a new amino acid to the elongating protein chain.

Spectrum

Good: Atypicals, *Haemophilus influenzae*, *Moraxella catarrhalis, Helicobacter pylori, Mycobacterium avium*

Moderate: S pneumoniae, *Streptococcus pyogenes*

Poor: Staphylococci, enteric GNRs (azithromycin > clarithromycin), anaerobes, enterococci

Adverse Effects

Gastrointestinal: Significant GI adverse effects (nausea, vomiting, diarrhea) have been associated with the macrolides. Erythromycin is the worst offender—it is employed as a prokinetic agent for patients with impaired GI motility.

Hepatic: Rare but serious adverse hepatic events have been associated with the macrolides.

Cardiac: Prolongation of the QT interval has been seen with the macrolides, again most commonly with erythromycin. Use with caution in patients with preexisting heart conditions, those on antiarrhythmic drugs, or those taking interacting drugs (see the next section).

IMPORTANT FACTS

- ***Drug interaction alert!*** These drugs (with the exception of azithromycin) are potent inhibitors of drug-metabolizing cytochrome P450 enzymes. Be sure to screen your patient's regimen before starting these agents.
- Azithromycin has a prolonged half-life such that a short course may be adequate for most infections. This led to the development of the Z-pak and the extended-release, single-dose Zmax. Although the Z-pak mantra of "5 days of medication that last as long as 10" is true, it is also true that many infections can be treated with 5 days of any medication, and 10 days is longer than most people need.
- Prevpac is a combination of drugs prescribed for eradication of *H pylori* and the treatment of peptic ulcer disease. In addition to clarithromycin and lansoprazole, it contains amoxicillin. Be sure to screen patients for both beta-lactam allergies and drug interactions before administering it.
- The spectrum of activity of macrolides makes them an ideal choice for the treatment of community-acquired pneumonia (CAP), but the high rates of resistance in *S pneumoniae* make them risky choices as monotherapy for patients with an infection that is any worse than mild. Take CAP seriously and avoid using a macrolide alone for most patients. Treat your more fragile patients with something else or add a beta-lactam active against *S pneumoniae*.

What They're Good For

Upper and lower respiratory tract infections, chlamydia, atypical mycobacterial infections, and traveler's diarrhea (azithromycin). Clarithromycin is a key component in the treatment of *H pylori*–induced GI ulcer disease in combination with other drugs and acid-suppressive agents.

Don’t Forget!

Sure, macrolides are good respiratory tract drugs and are relatively benign, but do you really need to be treating your patient’s nonspecific (possibly viral) cough and cold with any antibiotic? Besides causing possible adverse reactions and wallet toxicity, overuse of these drugs has contributed to increasing resistance. How about some decongestants, acetaminophen, and chicken soup instead?

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OXAZOLIDINONES

Agents: *linezolid, tedizolid*

There are two oxazolidinones: linezolid and tedizolid. This difficult-to-pronounce drug class has many favorable characteristics, including broad gram-positive activity and excellent oral bioavailability. Differences between the agents appear to be minor, though linezolid is dosed twice daily and tedizolid is once daily.

Mechanism of Action

Oxazolidinones are protein synthesis inhibitors that bind to the 50S ribosomal subunit, blocking the formation of a stable 70S initiation complex and preventing translation. This binding site is distinct from other protein synthesis inhibitors.

Spectrum

Good: MSSA, MRSA, streptococci (including multidrug-resistant *Streptococcus pneumoniae*), enterococci (including VRE), *Nocardia*

Moderate: Some atypicals, *Mycobacterium tuberculosis*

Poor: All gram-negatives, anaerobes

Adverse Effects

Both drugs are generally well tolerated for short-term therapy, but they can cause bone marrow suppression, most commonly thrombocytopenia. Bone marrow suppression tends to occur after 2 or more weeks with linezolid therapy and warrants monitoring. Tedizolid seems to have the same effects, though studies of longer duration are limited. With linezolid, it is known that peripheral neuropathy or lactic acidosis may occur after even more prolonged therapy (months) because of toxicity to mitochondria.

IMPORTANT FACTS

- Linezolid and tedizolid have bioavailability of over 90% and oral formulations, which greatly increase their utility.
- Linezolid is an inhibitor of monoamine oxidase (MAO) and can cause serotonin syndrome when given concurrently with serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs)—avoid concurrent use if possible. Recent evidence has shown this reaction to be uncommon, but it does occur. Animal models have shown tedizolid to have minimal if any MAO inhibition, but human data is limited.
- Linezolid has dual hepatic and renal elimination, and doses do not need to be adjusted in cases of renal or hepatic dysfunction. Tedizolid is eliminated primarily by the liver and may not be sufficiently concentrated in the urine to treat UTIs.
- Tedizolid was studied as a 6-day therapy for skin and skin structure infections and was comparable to 10 days of linezolid. The short course is nice, but it is also true that shorter courses work with other drugs too.
- Linezolid had historically been very expensive, but is now generic and relatively inexpensive. Oral formulations of both drugs are less expensive and more convenient than home-infusion vancomycin and a nurse.

What They’re Good For

Infections caused by resistant gram-positive organisms such as MRSA and VRE. Linezolid is useful for pneumonia, skin and skin structure infections, UTIs, and other uses. Tedizolid is currently indicated only for skin and skin structure infections but may be useful for other infection types.

Don’t Forget!

Monitor patients for bone marrow suppression, particularly during long-term therapy. Avoid concurrent serotonergic drug use with linezolid, if possible. Remember that many SSRIs have long half-lives, so simply discontinuing SSRI use does not avoid a potential interaction. Monitor patients for signs and symptoms of serotonin syndrome if the interaction cannot be avoided.

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NITROIMIDAZOLES

Agents: *metronidazole*, tinidazole

Nitroimidazoles are around to clean up organisms that the big drug classes—penicillins, cephalosporins, fluoroquinolones, macrolides, etc.—for the most part miss. Worried about gut anaerobes? Metronidazole is there for you. Thinking about parasites in your patient with diarrhea? Try metronidazole or its cousin tinidazole, which has a spectrum of activity similar to that of metronidazole but is approved only for parasitic infections. Just remember the limitations of these drugs: They do not have adequate activity against aerobic bacteria—staphylococci, streptococci, *Escherichia coli*, and such.

Mechanism of Action

Anaerobic bacteria and protozoa—but not aerobic bacteria—activate a part of the nitroimidazole molecule that forms free radicals, which are thought to damage DNA and lead to cell death.

Spectrum: metronidazole

Good: Gram-negative and gram-positive anaerobes, including *Bacteroides, Fusobacterium*, and *Clostridium* species; protozoa, including *Trichomonas, Entamoeba,*

and *Giardia*

Moderate: Helicobacter pylori

Poor: Aerobic anything, some anaerobes that reside in the mouth or skin (*Peptostreptococcus, Actinomyces, Cutibacterium*)

Adverse Effects

Gastrointestinal: Nausea, vomiting, and diarrhea, along with a metallic taste, are not uncommon with metronidazole. More severe adverse reactions such as hepatitis and pancreatitis are rare.

Neurologic: Dose-related, reversible peripheral neuropathy is occasionally reported with metronidazole, as have very rare cases of confusion and seizures.

IMPORTANT FACTS

- Metronidazole has a reputation for causing a disulfiram-like reaction with the consumption of alcohol, because of its inhibition of aldehyde dehydrogenase. Though it is a common warning to abstain from alcohol while taking metronidazole, this interaction is probably not clinically relevant, and some recent guidelines have removed the warning. Much more concerning is the interaction with warfarin, whose anticoagulant properties are significantly potentiated by inhibition of warfarin metabolism. Careful monitoring is required, and warfarin dose reduction is likely to be necessary.
- Metronidazole has excellent (~100%) bioavailability and none of the drug-chelating concerns of the fluoroquinolones; thus, patients should be switched from IV to oral metronidazole as soon as they are tolerating oral medications.

What They’re Good For

Infections with documented or suspected abdominal anaerobic bacteria, with adjunctive coverage of aerobes by a second drug when necessary. They are also used for treatment of vaginal trichomoniasis and GI infections caused by susceptible protozoa (amebiasis, giardiasis, etc.). Metronidazole is also a component of therapy for *H pylori* GI ulcer disease in combination with other antibacterials and acid-suppressive drugs. It is also a treatment option for mild to moderate *Clostridioides difficile* infections, but is not first line therapy.

Don’t Forget!

The GI flora of humans is a delicate ecosystem—disturb it at your patient’s peril. Metronidazole’s effect on the normal (primarily anaerobic) GI flora can set up your patients for

colonization with nasty bugs such as vancomycin-resistant *Enterococcus* (VRE); determine whether you really need anaerobic coverage.

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NITROFURANS AND FOSFOMYCIN

Agents: nitrofurantoin, fosfomycin

With the rise in resistance among common urinary tract pathogens (primarily *Escherichia coli*), first among TMP/SMX and more recently among the fluoroquinolones, clinicians are left searching for an alternative to treat their patients with uncomplicated cystitis. Nitrofurantoin and fosfomycin, although structurally dissimilar with different mechanisms of action, are two agents that have similar clinical niches. They have retained excellent activity against *E coli* (>90% in most studies) and have adequate coverage of other common community-acquired urinary tract pathogens. Their utility is limited to infections of the lower urinary tract, however, because of pharmacokinetic limitations. Thus, nitrofurantoin and fosfomycin should not be used for more severe urinary tract infections (UTIs) such as pyelonephritis and urosepsis. Intravenous fosfomycin is available in some other countries and is used for more severe gram-negative rod (GNR) infections, but because it is not presently available in the United States, we will not cover it here.

Mechanism of Action

Fosfomycin inhibits bacterial cell wall synthesis in a different way from beta-lactams and glycopeptides, preventing the production of the building blocks of peptidoglycan. The mechanism of action of nitrofurantoin is not well characterized.

Spectrum

Good: E coli, Staphylococcus saprophyticus

Moderate: Citrobacter, Klebsiella, Proteus, enterococci, *Serratia* (fosfomycin)

Poor: Acinetobacter, Pseudomonas

Adverse Effects

Gastrointestinal: Nausea and vomiting are occasionally reported. Taking the drugs with food may decrease these effects.

Pulmonary: Nitrofurantoin can cause very rare but serious pulmonary toxicity of two forms. First is an acute pneumonitis manifesting as cough, fever, and dyspnea. This form typically resolves soon after the drug is discontinued. Second, a chronic pulmonary fibrosis can occur, most commonly with prolonged nitrofurantoin therapy; recovery of lung function is limited after drug discontinuation.

IMPORTANT FACTS

- It bears repeating: Nitrofurantoin and fosfomycin in the formulations available in the United States are ineffective for infections outside of the lower urinary tract. The drugs require high concentrations for antimicrobial activity, and these are reached only where they concentrate in the urine. *Note:* This also means that in patients who have significant renal dysfunction (e.g., a creatinine clearance of less than 50 mL/min), there may be insufficient accumulation of the drug in the urine for activity. Nitrofurantoin in particular should be avoided in these patients.
- Nitrofurantoin comes in two formulations: a crystalline form (Macrodantin) and a macrocrystalline/monohydrate form (Macrobid). The former is dosed four times a day, and the latter twice a day. Guess which one patients prefer?
- Fosfomycin is only available in the United States as a powder that patients add to water before taking. An intravenous formulation that can be used for indications beyond UTIs is available in other countries and may become available in the United States at some point.
- A study of nitrofurantoin showed that it can be used for 5 days instead of the traditional 7-day regimen. This shorter regimen may make nitrofurantoin therapy more palatable for patients who are used to 3-day courses of other UTI drugs (TMP/SMX and fluoroquinolones). Fosfomycin is used for an even shorter duration: Its approved regimen for treatment of uncomplicated cystitis is a single dose. However, a study compared these

drugs for UTIs and found that 5 days of nitrofurantoin was more effective than a single-dose of fosfomycin.

What It's Good For

Treatment of uncomplicated cystitis in patients with adequate renal function (nitrofurantoin and fosfomycin) and prophylaxis against recurrent uncomplicated lower UTI (nitrofurantoin).

Don't Forget!

To repeat: Do not use these drugs in anything but cystitis. Nitrofurantoin or fosfomycin use in pyelonephritis or urosepsis is a treatment failure waiting to happen.

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STREPTOGRAMINS

Agent: *quinupristin/dalfopristin*

The increase in resistance to antibiotics among staphylococci and enterococci that began surging two decades ago led to pharmaceutical companies increasing the development of drugs to combat these resistant infections. One of the first of the newer drugs to treat vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) infections was quinupristin/dalfopristin. These drugs are two different streptogramins given in a combined formulation. Though each separate streptogramin is bacteriostatic, when given together they act *syner*gistically to give bacteri*cid*al activity against some gram-positive cocci—hence, the brand name of this drug: Synercid. Quinupristin/dalfopristin initially enjoyed frequent use, particularly to treat VRE infections, but its use has lessened as other agents have come on the market. Other streptogramins have been developed and are used in animals as growth promoters, a questionable but common practice in modern agriculture (where >50% of US antibiotics are used).

Mechanism of Action

Quinupristin and dalfopristin bind to different sites on the 50S subunit of the bacterial ribosome to prevent bacterial protein synthesis.

Spectrum

Good: MSSA, MRSA, streptococci, *Enterococcus faecium* (including vancomycin-resistant strains)

Poor: Enterococcus faecalis, anything gram negative

Adverse Effects

Quinupristin/dalfopristin can cause phlebitis and ideally should be administered via a central line. It is also associated with a high incidence of myalgias and arthralgias, which can limit tolerance to therapy. Quinupristin/dalfopristin also inhibits cytochrome P450 3A4, so clinicians need to be aware of potential drug interactions.

IMPORTANT FACTS

- Quinupristin/dalfopristin must be mixed and administered with 5% dextrose in water (D^5W) solutions only. When mixed with normal saline, the drug becomes insoluble and can crystallize, even when a patient's IV line is flushed with saline. Be sure that your patient's nurses know how to flush the line with D^5W or another saline-free diluent (since saline is commonly used for this). The drug is not available orally.
- The arthralgias and myalgias associated with quinupristin/dalfopristin are significant and should not be underestimated. It may be possible to decrease their severity by decreasing the dose, but this could compromise efficacy.
- The indication for the treatment of vancomycin-resistant *E faecium* infections was removed from the labeling of quinuprisin/dalfopristin due to a lack of follow-up data after the initial approval. It is no longer considered a first-line therapy for these infections.

What It's Good For

Infections caused by MRSA or *E faecium* in patients not responding to or intolerant of other medications.

Don't Forget!

Quinupristin/dalfopristin is not active against *E faecalis*. Between the two most common clinical species of *Enterococcus* (*E faecalis* and *E faecium*), *E faecalis* is more common in most hospitals, but it is less likely to be resistant to vancomycin. For this reason, quinupristin/dalfopristin is better employed as a definitive therapy than an empiric therapy for enterococci unless you strongly suspect *E faecium* infection. Linezolid and daptomycin do not have this issue and are better therapy options for the majority of patients.

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CYCLIC LIPOPEPTIDES

Agent: *daptomycin*

Daptomycin is the only cyclic lipopeptide that has made its way onto the market. It has a unique mechanism of action and target compared with other antibiotics. Daptomycin binds to the cell membrane of gram-positive bacteria, weakening it and allowing essential ions to leak out of the organism. This leads to a rapid depolarization of the membrane potential and cessation of needed cell processes, leading to cell death. Instead of blowing the bacteria apart as beta-lactams do, daptomycin leaves the dead bacteria intact.

Mechanism of Action

Daptomycin inserts into the cell membrane of gram-positive organisms, leading to the leakage of intracellular cations that maintain membrane polarization. The result is rapid depolarization and cell death.

Spectrum

Good: MSSA, MRSA, streptococci

Moderate to Good: Enterococci, including VRE

Poor: Anything gram negative

Adverse Effects

Daptomycin has effects on skeletal muscle that can manifest (rarely) as muscle pain or weakness, or possibly rhabdomyolysis. To monitor for this effect, creatine kinase (CK) concentrations should be checked weekly while a patient is on therapy. This toxicity can be decreased by administering the drug no more than once daily and by adjusting the interval in renal dysfunction. Eosinophilic pneumonia has been reported in patients on daptomycin therapy.

IMPORTANT FACTS

- Daptomycin is active against many resistant gram-positive organisms, including VRE and MRSA. It has been proven effective in staphylococcal endocarditis (specifically right-sided endocarditis), an indication that few antibiotics have.
- Before using daptomycin for your patient, ensure that the lab tests the isolate for daptomycin susceptibility. Resistance to daptomycin is uncommon in *Staphylococcus aureus*, but it does occur. Because a standard minimum inhibitory concentration (MIC) for resistance has not been defined for *S aureus* (there is only a breakpoint for what is "susceptible"), labs may report isolates as "nonsusceptible" or, worse, not report them at all if they do not fall into the susceptible range. In contrast, for *Enterococcus faecium*, a category of "susceptible" doesn't exist—only "susceptible, dose-dependent" and "resistant." This is meant to highlight that higher doses are frequently required in treatment of this pathogen.
- Though it penetrates lung tissue very well, daptomycin cannot be used to treat pneumonia. Human pulmonary surfactant binds to daptomycin, rendering it inactive. Early clinical trials showed poor outcomes in daptomycin-treated pneumonia patients.
- Daptomycin's FDA-approved dosing is 4–6 mg/kg/d. Studies suggest that higher doses than this range may be more effective without causing substantially more toxicity. Thus, in practice doses of 8–10 mg/kg/d may be used for severe staphylococcal infections and doses of 10–12 mg/kg/d are recommended in guidelines for enterococcal endocarditis.
- Some studies have shown synergism between daptomycin and some beta-lactams, even in beta-lactam–resistant organisms like MRSA and VRE. It may seem like a weird combination, but there is a logical mechanism behind it, which we will explain in our next text, *Antibiotics Complexified*.

What It's Good For

Skin and skin structure infections, bacteremia, endocarditis, and urinary tract infections caused by resistant gram-positive organisms. Daptomycin is also used in other infections caused by these organisms but notably cannot be used for pneumonia.

Don’t Forget!

Monitor CK concentrations and renal function for patients taking daptomycin, particularly if they are on other drugs toxic to skeletal muscle, like 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

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19

FOLATE ANTAGONISTS

Agents: *trimethoprim/sulfamethoxazole*, dapsone, pyrimethamine, sulfadiazine

The combination drug trimethoprim/sulfamethoxazole (TMP/SMX) is the most widely used folate antagonist, active against both bacterial and parasitic/fungal infections. TMP/SMX was once considered a broad-spectrum antibacterial drug but has since fallen victim to the relentless march of antibiotic resistance; however, it is still a drug of choice for a number of indications. Resistance varies considerably by geographic region, so consider your local antibiogram before using TMP/SMX as empiric therapy. Dapsone, pyrimethamine, and sulfadiazine are used primarily against parasitic and fungal infections. The following information refers to TMP/SMX except where noted.

Mechanism of Action

These drugs inhibit steps in the folate biosynthesis pathway, depleting the pool of nucleosides and ultimately leading to inhibition of DNA synthesis in susceptible organisms.

Spectrum

Good: Staphylococcus aureus (including many MRSA strains), *Haemophilus influenzae,*

Stenotrophomonas maltophilia, Listeria, Pneumocystis jirovecii, *Toxoplasma gondii* (pyrimethamine and sulfadiazine)

Moderate: Enteric GNRs, *Streptococcus pneumoniae*, *Salmonella*, *Shigella, Nocardia, Streptococcus pyogenes*

Poor: Pseudomonas, enterococci, anaerobes

Adverse Effects

Dermatologic: TMP/SMX frequently causes rash, usually because of the sulfamethoxazole component. Rash is much more common in HIV/AIDS patients. Although these rashes are usually not severe, life-threatening dermatologic reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome also occur.

Hematologic: A primarily dose-dependent bone-marrow suppression can be seen with TMP/SMX, especially at the higher doses used to treat *Pneumocystis* infections. Pyrimethamine works similarly and also causes this, though more frequently. Leucovorin prevents this toxicity and is commonly given with pyrimethamine (but rarely with TMP/SMX).

Renal: Confusingly, TMP/SMX can cause both true and pseudo-renal failure. Crystalluria and acute interstitial nephritis (AIN) caused by the SMX component can lead to acute renal failure; however, the blockade of creatinine secretion by TMP can cause an increase in serum creatinine without a true decline in glomerular filtration rate. TMP can also cause hyperkalemia in a fashion similar to the potassium-sparing diuretics (e.g., triamterene).

IMPORTANT FACTS

- For years, TMP/SMX was standard first-line therapy for treatment of acute uncomplicated cystitis in women. Guidelines suggest, however, that in areas with local resistance rates greater than 15–20% in *Escherichia coli*, an alternative drug (e.g., nitrofurantoin) should be used. At a minimum TMP/SMX should not be used for empiric therapy of complicated UTI (pyelonephritis or urosepsis).
- TMP/SMX comes in a fixed 1:5 ratio of the two components. Dosing is usually based on the TMP component. The oral tablet comes in two strengths: single-strength (80:400 mg TMP:SMX) and double-strength (160:800 mg TMP:SMX). TMP/SMX has excellent oral bioavailability, allowing for conversion to oral therapy when patients are tolerating oral medications. If you see an oddly high or low dose being prescribed or recommended, be sure that the intended dose is correct.

- TMP/SMX has a significant drug interaction with warfarin, leading to higher-than-anticipated prothrombin times. TMP/SMX should be avoided in patients on warfarin if possible. If coadministration is absolutely necessary, careful monitoring of the patient's international normalized ratio (INR) is required.
- TMP/SMX is fairly insoluble in IV solutions, and relatively large volumes of diluent are needed for it to go into solution. Be aware that this fluid may be considerable, particularly for volume-overloaded patients such as those with heart failure.
- The predominant strain of MRSA in the US is very susceptible to TMP/SMX. This strain likes to cause skin infections with abscesses, often large ones. TMP/SMX is a good choice of therapy for staphylococcal skin infections, but abscesses must be drained.

What They're Good For

Treatment of uncomplicated lower UTIs (empirically in areas with low local resistance, definitively whenever susceptible), prophylaxis against recurrent UTIs, treatment of *Listeria* meningitis, treatment of and prophylaxis for *P jirovecii* pneumonia, and treatment of *Toxoplasma* encephalitis. TMP/SMX is also an alternative therapy for bacterial prostatitis, typhoid fever, and methicillin-resistant *S aureus* infections. Pyrimethamine and sulfadiazine are used in the treatment of toxoplasmosis. Dapsone is a sulfone antibiotic that may be tolerated by some patients with TMP/SMX allergies and is often used as an alternative agent for *Pneumocystis* prophylaxis in these patients.

Don't Forget!

Patients allergic to TMP/SMX are often flagged as having a broad "sulfa allergy." In most cases, patients can tolerate nonantimicrobial sulfas like furosemide, sulfadiazine, acetazolamide, hydrochlorothiazide, and glipizide, but should avoid other sulfa-containing antimicrobials. If patients have a severe TMP/SMX allergy such as Stevens-Johnson syndrome and require a sulfonamide-containing agent, consider having an allergist weigh in.

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LINCOSAMIDES

Agent: *clindamycin*

Clindamycin can be considered a mix of vancomycin and metronidazole; it has attributes of each drug, but it is not quite as good as either one alone. Clindamycin is an alternative when treatment requires gram-positive activity (as with beta-lactam allergies), but it has more variable activity than vancomycin against such pathogens as MRSA and *Streptococcus pyogenes*. Clindamycin also covers many anaerobic organisms, but there is a higher level of resistance among the gram-negative anaerobes (such as *Bacteroides fragilis*) than with metronidazole. Because of these limitations and clindamycin's tendency to cause GI toxicity, it is best used empirically for nonsevere infections of the skin and oral cavity, or as definitive therapy when susceptibilities are known.

Mechanism of Action

Clindamycin binds at a site on the 50S ribosome right next to where the macrolides bind and acts similarly in preventing protein synthesis by preventing the ribosome from moving on to adding another amino acid in the protein chain.

Spectrum: clindamycin

Good: Many gram-positive anaerobes, *Plasmodium* species (malaria), *S pyogenes*

Moderate: Staphylococcus aureus (including many MRSA), *Streptococcus agalactiae,* gram-negative anaerobes, *Chlamydia trachomatis, Pneumocystis jirovecii, Actinomyces, Toxoplasma*

Poor: Enterococci, *Clostridioides difficile*, gram-negative aerobes

Adverse Effects

Gastrointestinal: Diarrhea is one of the most common adverse effects associated with clindamycin. Clindamycin itself can cause relatively benign, self-limited diarrhea or can result in more severe diarrhea resulting from superinfection with *C difficile*. Although *C difficile*–associated diarrhea and colitis can occur with any antibiotic, the incidence in patients who receive clindamycin therapy is among the highest. Patients with diarrhea need evaluation for *C difficile* disease, especially if it is severe, is associated with fever, or persists after clindamycin therapy.

Dermatologic: Rash may occur with clindamycin, very rarely with severe manifestations such as Stevens-Johnson syndrome.

IMPORTANT FACTS

- Clindamycin is a reasonable alternative drug for the treatment of staphylococcal infections; however, care must be taken in interpreting the antibiotic susceptibility of these isolates. A significant proportion of organisms that are reported as clindamycin-susceptible but erythromycin-resistant may harbor a gene for resistance that may lead to high-level clindamycin resistance during therapy. Erythromycin-resistant, clindamycin-susceptible strains should be screened with a D-test (the microbiology lab will know what you mean) before using clindamycin. If the D-test is positive, then inducible clindamycin resistance is present and clindamycin should not be used.
- Clindamycin's inhibition of protein synthesis and activity against organisms in stationary-phase growth has been utilized in the treatment of necrotizing fasciitis and other toxin-mediated diseases. Consider the addition of clindamycin to beta-lactam–based therapy when treating these types of infections.
- Clindamycin is nearly 100% orally bioavailable, but oral doses are generally lower than IV doses in order to improve GI tolerance.
- Many community-acquired MRSA infections are susceptible to clindamycin, but not as many as are susceptible to TMP/SMX.

What It’s Good For

Treatment of skin and soft-tissue infections, infections of the oral cavity, and anaerobic intra-abdominal infections. It is used topically in the treatment of acne. Clindamycin is a second-line agent (in combination with primaquine) in the treatment of *P jirovecii* pneumonia. It is also used to treat malaria (in combination with other drugs), to treat bacterial vaginosis, and in the prophylaxis of bacterial endocarditis.

Don’t Forget!

Almost all antibiotics have been associated with an increased risk of *C difficile* disease; however, some studies suggest that clindamycin may confer an especially high risk. (Note that this is a popular board exam question.) Although it is a convenient and relatively well-tolerated drug, clindamycin should not be used lightly because of this risk.

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21
POLYMYXINS

Agents: *colistin (colistimethate sodium), polymyxin B*

Polymyxins are an older class of antibiotics that had nearly vanished from systemic use years ago in favor of the “safer” aminoglycosides. Unfortunately, the continuous evolution of bacterial resistance has forced the medical community to revisit the use of colistin and polymyxin B in the treatment of resistant gram-negative infections. This is problematic because these drugs have not been evaluated with the rigor of the modern drug approval process, and pharmacokinetic and efficacy data on their use are limited. However, they have a role as a last-ditch treatment of infections caused by highly resistant gram-negative organisms such as *Acinetobacter baumannii, Pseudomonas aeruginosa,* and carbapenem-resistant Enterobacterales (CRE) such as *Klebsiella pneumoniae*.

Mechanism of Action

Polymyxins bind to the outer membrane of gram-negative bacteria, leading to disruption of membrane stability and leakage of cellular contents.

Spectrum

Good: Many GNRs, including multidrug-resistant *A baumannii*, *P aeruginosa*, and *K*

pneumoniae

Moderate: Stenotrophomonas maltophilia

Poor: All gram-positive organisms, anaerobes, *Proteus, Providencia, Burkholderia, Serratia*, and gram-negative cocci

Adverse Effects

Renal: The most common adverse effect is nephrotoxicity due to acute tubular necrosis. Acute kidney injury commonly occurs in clinical use, though the incidence of polymyxin-induced toxicity is hard to estimate because most recent studies of polymyxins are noncomparative evaluations of salvage therapies in very ill patients. Several studies suggest that polymyxin B is less nephrotoxic than colistin. Avoid concomitant nephrotoxins if possible.

Neurological: Neurotoxicity is less common. It can manifest as dizziness, weakness, paresthesias, or mental status changes. Neuromuscular blockade can also occur and may lead to fatal respiratory arrest.

IMPORTANT FACTS

- Colistin and polymyxin B are very similar drugs. Colistin may be more active, but to be given systemically it is administered as colistimethate sodium. Colistimethate is then converted into active colistin in the body. Colistimethate is renally cleared, and only the proportion that is not cleared is converted to colistin. In the United States, it is typically dosed as milligrams of “colistin base activity” (~400 mg colistimethate = 150 mg of colistin base activity), though the actual amount that is systemically active differs in each patient. Colistin itself is not used systemically. When most references refer to “colistin” (including this one), they are referring to “colistimethate sodium.”
- One area where polymyxins differ is in pharmacokinetics. As previously mentioned, colistin is given as a renally eliminated prodrug. Polymyxin B is given in its active form and has more predictable pharmacokinetics. Both drugs should be given with loading doses.
- Polymyxin B is not eliminated renally, and modern pharmacokinetic studies suggest that it should not be dose adjusted in renal dysfunction, which goes against recommendations in the package insert. It also is unlikely to be successful in treating urinary tract infections (UTIs).
- To further confound colistin use, different standards of dosing are used by different countries. The US formulation is dosed in milligrams of colistin base activity, whereas

Europe and many other parts of the world dose in international units. When comparing, it is important to know that 1 mg of colistin base activity is equivalent to about 30,000 units. It actually calculates to ~33,333 units, but many references round this number.

- There are two ways of summarizing colistin dosing:
  - 1,000,000 units ≈ 80 mg colistimethate ≈ 30 mg colistin base activity
  - 1 mg colistin base activity ≈ 2.7 mg colistimethate ≈ 30,000 units
- Never prescribe or recommend colistin doses in terms of milligrams of colistimethate. A misinterpretation can be fatal.
- Speaking of confounding dosing standards, polymyxin B is dosed in either milligrams or international units. Note that 1 mg = 10,000 units.
- Because polymyxin drugs are generally last-line antibiotics, they are frequently used in combination with other drugs. Various combinations of colistin and other drugs such as rifampin and meropenem may be better than colistin use alone; this is an area of active study.
- The oral formulation of colistin is given only for bowel decontamination, such as before GI surgery. Don't try to convert someone from IV to po colistin to treat a systemic infection.
- Aerosolized polymyxins are used to decrease colonization with gram-negative bacteria (principally *Pseudomonas*) in some patients, particularly those with cystic fibrosis. They should be prepared just before administration. Some experts have used aerosolized drugs to treat pneumonia also, though evidence for this practice is weak.

What They're Good For

Polymyxins are useful in the treatment of multidrug-resistant gram-negative infections, including pneumonia, bacteremia, sepsis, and complicated UTIs. Generally, polymyxin B is preferred for infections outside of the urinary tract, whereas colistin is preferred for UTIs. Because polymyxins are poorly studied in many of these disease states, other drugs should be used if pathogens are susceptible.

Don't Forget!

Although estimates of polymyxin nephrotoxicity vary, the incidence is substantial, particularly in critically ill patients who may not be able to tolerate the renal insult. Monitor renal function closely in patients receiving polymyxins and avoid other nephrotoxins if possible, including vancomycin. Above all, avoid using polymyxins unless you absolutely have to. Better therapies are usually available.

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CLOSTRIDIOIDES DIFFICILE–SPECIFIC AGENTS

Agent: fidaxomicin, *bezlotoxumab*

Fidaxomicin and bezlotoxumab are two drugs that have only one thing in common: They only treat *Clostridioides difficile* infections. Fidaxomicin is a nonabsorbed macrocyclic antibiotic with a narrow spectrum that is ideal for treating infections caused by *C difficile* because it is sparing to the normal flora of the GI tract, allowing it to be restored during therapy. Bezlotoxumab is a monoclonal antibody that renders a toxin produced by *C difficile* inactive, decreasing the risk of recurrent infections.

Mechanism of Action

Fidaxomicin is a ribosomal protein synthesis inhibitor that is bactericidal. It is classified as a macrolide by the US FDA, but unlike other macrolides, it is not absorbed in the GI tract and is able to kill susceptible organisms.

Bezlotoxumab binds to toxin B (bezlotoxumab) produced by toxigenic *C difficile*.

Spectrum

Good: C difficile

Poor: Anything else

Adverse Effects

As a nonabsorbed antibiotic, fidaxomicin would be expected to have few systemic adverse effects. Most of the adverse effects reported in clinical trials are associated with *C difficile* infection, including nausea, diarrhea, abdominal pain, and cramping. Bezlotoxumab was well-tolerated in its studies, but patients with a history of heart failure had adverse effects more frequently than placebo patients.

IMPORTANT FACTS

- In a clinical trial comparing it with vancomycin capsules, fidaxomicin showed similar clinical efficacy to oral vancomycin. However, it was superior in preventing recurrences of *C difficile* infection. Recently updated guidelines recommend it as a first-line agent.
- The advantages of fidaxomicin in sparing the normal flora of the GI tract are likely negated when it is coadministered with oral vancomycin or metronidazole. Two drugs are not always better than one, and these combinations should be avoided.
- Since bezlotoxumab only binds toxins and does not kill *C difficile* directly; patients need to receive antibacterials that are treating *C difficile* as well (e.g., vancomycin or fidaxomicin). Bezlotoxumab can be given at any time during the treatment course, with a similar reduction in recurrence.
- Patients who received bezlotoxumab in clinical trials had less recurrence that those who didn't, but it did not change the initial cure rate. It is best used in patients with a high risk of recurrence.
- Fidaxomicin and bezlotoxumab are both expensive. Patient assistance programs are available to help acquire drugs for those who need them. The high cost of the drug is cheaper than an admission for *C difficile* relapse, but we have to acknowledge that a wonderful drug is not wonderful for a patient who can't take it due to cost.

What It's Good For

Clostridium difficile infections, ranging from diarrhea to pseudomembranous colitis.

Don't Forget!

Fidaxomicin and bezlotoxumab have an important benefit in lowering *C difficile* infection recurrence, but cost necessitates careful determination of which patients are most likely to benefit from them.

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PART 3

ANTIMYCOBACTERIAL DRUGS

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23

ANTIMYCOBACTERIAL DRUGS

INTRODUCTION TO ANTIMYCOBACTERIAL DRUGS

Tuberculosis (TB), the disease caused by *Mycobacterium tuberculosis*, is one of the world's most formidable infections. Tuberculosis and other mycobacterial diseases are difficult to treat for several reasons. Mycobacteria replicate more slowly than "typical" bacteria such as *Escherichia coli* or *Staphylococcus aureus*. This may seem to make the disease easier to control, but it makes pharmacotherapy more difficult because rapidly dividing cells are most metabolically active and therefore more susceptible to antibiotic chemotherapy.

Mycobacteria can also exist in a dormant state, making them resistant to nearly all antibiotics. In the host, they live inside human cells, and therefore antimicrobials that have poor intracellular penetration are less effective. Mycobacteria also have cell walls that are structurally different from typical gram-positive and gram-negative bacteria. The outermost layer of mycobacteria consists of phospholipids and mycolic acids that make a waxy layer that resists penetration from antibiotics. Arabinogalactan and peptidoglycan are polysaccharide components of the cell wall, but the peptidoglycan is not accessible to beta-lactam antibiotics, and they are poorly active. **FIGURE 23-1** shows the basic structure of mycobacteria.

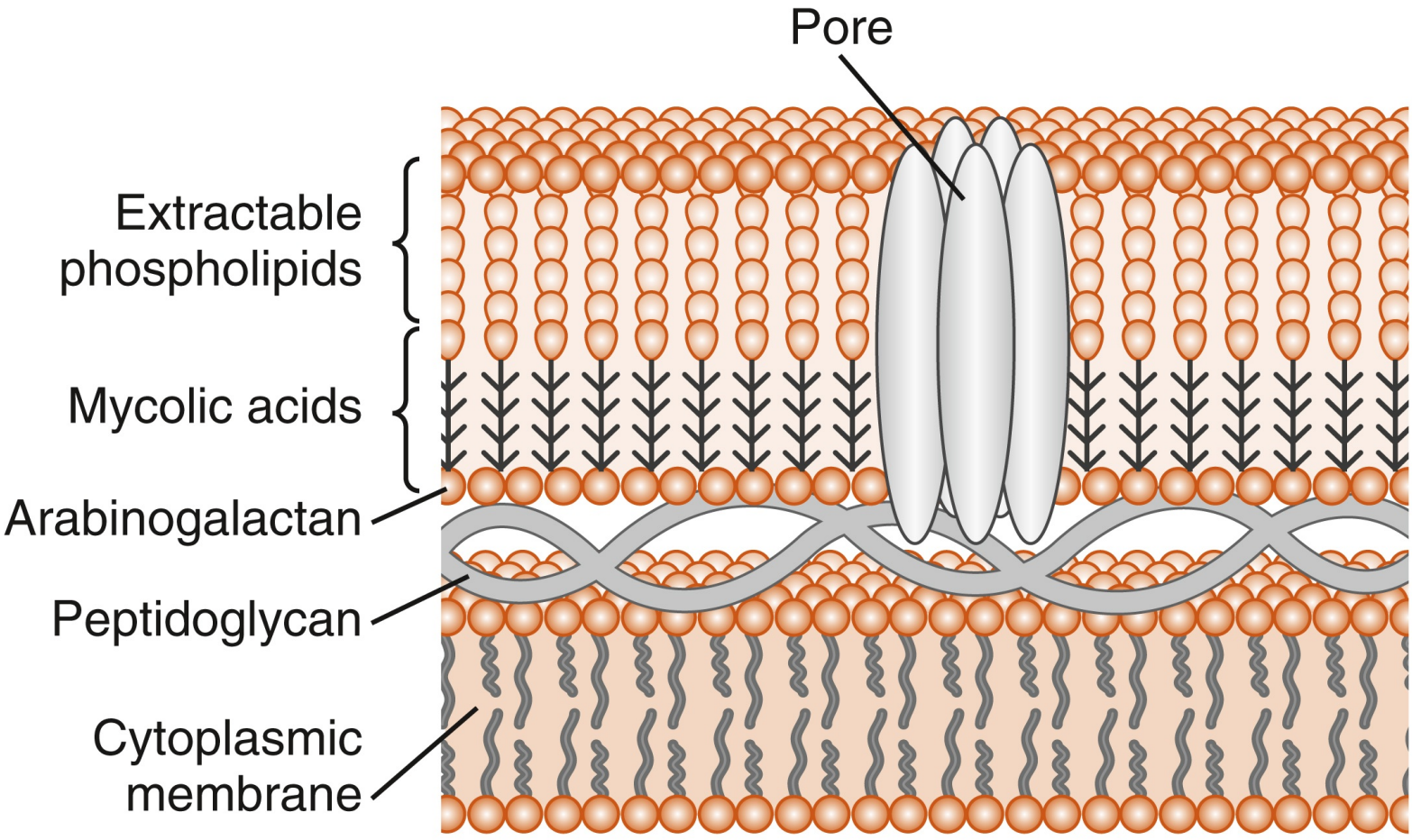

FIGURE 23-1 Mycobacterial Cell Wall

Description

The pharmacotherapy of mycobacterial disease is complex. Combinations of drugs are always given for patients with active disease to minimize the development of resistance and shorten the duration of therapy. These combinations frequently have pharmacokinetic drug interactions with both each other and other medications that the patient is on (in part because immunocompromised patients are particularly vulnerable to mycobacterial disease and tend to be on drugs with many interactions). Because mycobacteria grow slowly, standard susceptibility testing takes weeks instead of days to perform, so empiric regimens are often given for extended durations. Newer technology can shorten this duration, but is not yet widely used. For TB, the standard of care for patients with active infections is to start with a four-drug regimen, so compliance and careful monitoring for drug interactions are important.

This section discusses first-line drugs for TB and nontuberculous mycobacterial (NTM) infections, focusing on *Mycobacterium avium-intracellulare* complex (MAC). A number of other agents may also be employed (**TABLE 23-1**), many of which are discussed elsewhere in the book, and some second-line and third-line drugs are available for treatment of drug-resistant disease. However, because the treatment of multidrug-resistant tuberculosis (MDR-TB) requires an infectious diseases specialist to lead management, we omit further discussion of these agents from this text—there is nothing “simplified” about MDR-TB. It is particularly important to know the toxicities and potential drug interactions of the first-line agents for TB, since patients are exposed to these agents for months to years. Of note, because of their frequent use as combination regimens, you may see these agents referred to with a variety of abbreviations, as noted in Table 23-1. For example, the first-line combination of rifampin,

isoniazid, pyrazinamide, and ethambutol may be abbreviated as “RIPE” or “HRZE.” Yes, the order of the drugs is different in the abbreviations; that’s just how it’s done. HRZE is increasingly used among TB professionals, but RIPE is catchier and will likely hang around awhile.

TABLE 23-1 Agents for Treatment of Mycobacterial Infections

Drug (Route) [Abbreviations]	Uses and Characteristics
Rifampin (IV/po) [RIF, R] Rifabutin (po) [Rfb] Rifapentine (po) [Rfp]	-Used for TB and NTM infections -Described in Chapter 24
Isoniazid (IV/po) [INH, I, H]	-Used for TB infections -Described in Chapter 25
Pyrazinamide (po) [PZA, P, Z]	-Used for TB infections -Described in Chapter 26
Ethambutol (po) [EMB, E]	-Used for TB and NTM infections -Described in Chapter 27
Moxifloxacin (IV/po) [Mfx] Levofloxacin (IV/po) [Lfx]	-Used for TB and NTM infections -Described in Chapter 10
Azithromycin (IV/po) [Azm] Clarithromycin (po) [Clr]	-Used for TB and NTM infections -Described in Chapter 13
Linezolid (IV/po) [Lzd]	-Used for TB and NTM infections -Described in Chapter 14
Amikacin (IV/IM) [Am] Streptomycin (IV/IM) [S]	-Used for TB and NTM infections -Described in Chapter 11
Bedaquiline (po) [Bdq]	-Used for MDR-TB -QT prolongation -Drug-drug interactions
Clofazimine (po) [Cfz]	-Used for MDR-TB and NTM infections -Skin pigmentation changes -Hepatotoxicity
Cycloserine (po) [Cs]	-Used for MDR-TB -Psychiatric effects -Neuropathy
Ethionamide (po)	-Used for MDR-TB -GI Intolerance -Dysglycemia
Delamanid (po) [Dlm]	-Used for MDR-TB -QT prolongation -Drug-drug interactions

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RIFAMYCINS

Agents: *rifampin* (aka rifampicin), rifabutin, rifapentine, rifaximin (not used for mycobacterial disease)

The rifamycins are cornerstones of therapy for both tuberculosis (TB) and *Mycobacterium avium-intracellulare* (MAC). Rifampin (or rifampicin, as it is known to Europeans) is one of the two most important drugs in TB pharmacotherapy. The rifamycins are potent inducers of the cytochrome P450 system, and patients receiving them should *always* be screened for drug interactions. In addition to their activity against mycobacteria, rifamycins are active against many “typical” bacteria as well and are sometimes added to other therapies, particularly to treat difficult methicillin-resistant *Staphylococcus aureus* (MRSA) infections. However, rifamycins have a very low genetic barrier to development of resistance and are thus almost always used as part of a multidrug regimen for treatment. The primary exception is in treatment of latent TB infection, where the organism burden is low and development of resistance is less of a concern.

Mechanism of Action

Rifamycins are protein synthesis inhibitors that work by inhibiting RNA polymerase, preventing transcription by blocking the production of messenger RNA. This separates them from other protein synthesis inhibitors, which inhibit translation.

Spectrum

Good: Most mycobacteria (some nontuberculous mycobacterial [NTM] infections are rifamycin-resistant, and there is rare resistance to rifamycins among *M tuberculosis*)

Moderate: Staphylococcus, Enterobacterales (when used in multidrug combinations)

Poor: "Typical" bacteria as monotherapy

Adverse Effects

Rifamycins are generally well-tolerated drugs that are most notorious for their potent CYP450-inducing effects. Their potent induction of metabolism can lead to subtherapeutic concentrations of other drugs, which can manifest with devastating clinical consequences, such as loss of seizure control (anticonvulsants) or organ rejection (antirejection agents). Rifamycins characteristically discolor secretions (urine, tears, etc) orange-red and can actually stain contact lenses, which should not be worn during rifamycin therapy. Otherwise, this effect is nonpermanent and not harmful, which patients appreciate knowing. Rifamycins can also cause hepatotoxicity. Other side effects include rash, nausea, vomiting, and hypersensitivity (often fever). Rifabutin specifically is associated with leukopenia and optic neuritis, particularly if its levels are elevated as a result of drug-drug interactions.

IMPORTANT FACTS

- Rifampin is a drug of choice for TB, whereas rifabutin is a drug of choice for MAC, although both drugs have activity against both pathogens. MAC infections are most common in patients with HIV, who are often taking antiretroviral therapy that is metabolized by CYP450. Because rifabutin has somewhat less-potent CYP450-inducing effects than rifampin, it is more commonly used in MAC infections to minimize the impact of drug interactions in this population.
- Rifampin (or rifabutin) is one of the two most important drugs in the treatment of TB (the other being isoniazid). If an isolate of *Mycobacterium tuberculosis* is rifampin-resistant, then the likelihood of successful pharmacotherapy is lower, and more complicated regimens must be used for a longer duration.
- Rifabutin induces CYP450 metabolism less potently than rifampin does, but it is still a potent inducer and requires careful review of potential consequences of its interaction on a patient's drug regimen. Unlike rifampin and rifapentine, rifabutin is also metabolized by P450 enzymes, and thus drugs that are enzyme inhibitors can increase rifabutin levels, potentially leading to toxicity.
- Rifapentine is given once weekly. It shares susceptibility with rifampin and rifabutin, meaning that if an isolate is resistant to one drug, it is likely resistant to all of them. Recent

guidelines recommend rifapentine in combination with isoniazid as a once-weekly therapy for latent TB, and it is occasionally used in combination regimens for active TB.

- Rifaximin is a nonabsorbed rifamycin used only in the treatment or prevention of GI conditions. It is not used for mycobacterial diseases and is listed here only for completeness.
- As previously noted, rifamycins should not be used as monotherapy for most indications outside of latent TB infection, so carefully scrutinize orders where a rifamycin doesn't have a "buddy."

What They're Good For

Treatment of active TB and MAC, in combination with other agents; latent TB; and selected bacterial infections (most notably bacterial infections involving prosthetic material—such as an artificial hip or heart valve—in combination with standard antibacterials).

Don't Forget!

Ensure that patients are informed that their urine and other secretions may turn orange or red. That's a surprise that most people don't want and could lead to completely unnecessary emergency room visits!

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25
ISONIAZID

Agent: *isoniazid*

Isoniazid is active only against *Mycobacterium tuberculosis* and the related *Mycobacterium kansasii*, but it is one of the two most important drugs in tuberculosis (TB) pharmacotherapy (the other being rifampin), owing to its effectiveness against both actively growing and dormant mycobacteria. It is used in the treatment of both active and latent TB.

Mechanism of Action

Isoniazid prevents the synthesis of mycolic acids in the cell wall by inhibiting enzymes that catalyze their production.

Spectrum

Active only against *M tuberculosis* and *M kansasii.*

Adverse Effects

Like several other TB medications, hepatotoxicity is a concern. Many patients will experience asymptomatic elevations in liver transaminases early in therapy. In most cases, these will resolve on their own, and the patient can complete treatment. However, if the enzyme levels

are many times the upper limit of normal and/or the patient experience symptoms of hepatitis (nausea, abdominal pain, jaundice), the drug needs to be stopped to prevent severe liver damage. Isoniazid's other characteristic adverse reaction is peripheral neuropathy. This can be prevented by administering pyridoxine (vitamin B^6), which is recommended for patients at risk for developing neuropathy (alcohol use disorder, diabetics, pregnant women, alcohol abusers). Other neurotoxicities that are less common include optic neuritis and, rarely, seizures. Drug-induced lupus can also occur; this abates with the cessation of therapy. Hypersensitivity can be seen, most commonly as rash or drug fever.

IMPORTANT FACTS

- Isoniazid was for many years the drug of choice for treatment of latent TB. It can be given as monotherapy for latent disease because the burden of organisms is much lower than in active TB, where resistance can develop to monotherapy. However, since isoniazid-only regimens require 6–9 months of therapy, recent guidelines favor isoniazid-rifamycin combination or rifampin-only regimens, which can be given for 3 or 4 months, respectively.
- Isoniazid is a classic example of a drug with variable pharmacogenomic metabolism. "Rapid acetylators" of isoniazid metabolize it more quickly than "slow acetylators," but the clinical significance of this is limited. Genetic testing is not routinely performed before starting isoniazid.
- Isoniazid is bactericidal against growing mycobacteria but bacteriostatic against dormant mycobacteria.
- Patients should be advised not to drink alcohol while taking isoniazid. This has nothing to do with the common myth that alcohol decreases antibiotic effectiveness; it is to prevent an additive risk of hepatotoxicity.

What It's Good For

Isoniazid is a drug of choice for both active and latent TB. For treatment of active TB, it is typically part of a four-drug initial regimen, followed by consolidation with the combination of isoniazid and rifampin.

Don't Forget!

Although guidelines recommend adding pyridoxine for preventing neuropathy only in high-risk patients, there's no downside in recommending it to all your patients receiving isoniazid. Don't confuse pyridoxine with pyrazinamide (discussed in the next section) and assume that your patient is receiving both drugs when they are not. Most patients with TB should be taking both pyridoxine and pyrazinamide during the initial phase of therapy.

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PYRAZINAMIDE

Agent: pyrazinamide

Pyrazinamide is a first-line drug for the treatment of tuberculosis (TB). As part of the initial four-drug regimen for active TB, it enables the overall duration of therapy to be shortened from 9 months to 6 months. Pyrazinamide has bactericidal activity against even slow-growing *Mycobacterium tuberculosis*. It is generally used only in the first 2 months of TB therapy for drug-sensitive TB, but it may be used for longer durations in multidrug-resistant tuberculosis (MDR-TB) infections.

Mechanism of Action

Pyrazinamide is a prodrug with an unclear mechanism of action. In its active form it is thought to prevent the production of mycolic acids by inhibiting the enzyme fatty acid synthetase I, though it likely has other effects as well.

Spectrum

Active only against *M tuberculosis.*

Adverse Effects

The key adverse effects for pyrazinamide are hyperuricemia and hepatotoxicity. Hepatotoxicity (chiefly hepatitis) is dose-dependent and less common at the lower doses given today than the higher ones previously used. Hyperuricemia is predictable and can rarely precipitate gout, leading to withdrawal of pyrazinamide from the regimen and an extension of the duration of TB therapy. Arthralgias also occur and are separate from hyperuricemia; these can be managed with over-the-counter pain medications.

IMPORTANT FACTS

- Interestingly, pyrazinamide is active only in acidic environments (pH <6). This would be problematic for some diseases, but it is perfect for the caseous granulomas that active TB forms. It also works intracellularly in phagocytes.
- Be careful not to confuse this drug with pyridoxine, which most patients with active TB should also be taking to prevent isoniazid-induced peripheral neuropathy.

What It's Good For

Pyrazinamide's only use is as part of a combination therapy regimen for active TB.

Don't Forget!

Tell your patients to report any signs of hepatitis (dark urine, abdominal pain, loss of appetite) when they are on pyrazinamide.

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27
ETHAMBUTOL

Agent: ethambutol

Ethambutol is a first-line drug for the treatment of both active tuberculosis (TB) and *Mycobacterium avium-intracellulare* (MAC) infections. Like pyrazinamide, ethambutol is principally used in the initial four-drug phase of active TB, whereas in the treatment of MAC it is frequently administered for the entire duration of therapy.

Mechanism of Action

Ethambutol inhibits the enzyme arabinosyl transferase III, which blocks production of arabinogalactan. Because arabinogalactan is a component of the cell wall of mycobacteria but not “typical” bacteria, the microbial activity of ethambutol is limited to mycobacteria.

Spectrum

Mycobacterium tuberculosis, *Mycobacterium avium-intracellulare* complex, *Mycobacterium kansasii*

Adverse Effects

The characteristic adverse effects of ethambutol are optic neuropathies, often manifesting as

decreased visual acuity or the inability to differentiate red from green. The occurrence of this adverse effect is dependent on both the dose and duration of therapy. Monitoring is required to detect this problem to limit the extent of damage; full recovery of vision may or may not occur on drug discontinuation. Use of ethambutol in children younger than 5 years old is not recommended, because they are generally not able to reliably perform the vision tests needed for monitoring. Rash and drug fever occur uncommonly.

IMPORTANT FACTS

- Ethambutol is overall very well tolerated, and it is the one component of the “RIPE” or “RHZE” (rifampin, isoniazid, pyrazinamide, ethambutol) active TB regimen that is not associated with hepatotoxicity.
- Ethambutol can be used as a substitute for rifampin in patients who are unable to take that medication during the continuation phase (after 2 months) of active TB therapy. However, the duration of therapy has to be extended relative to what it would be with rifampin and isoniazid.
- Ethambutol is one of the primary first-line drugs (along with a macrolide and rifabutin) for treating MAC infections.

What It’s Good For

First-line therapy for both active TB and MAC infections. Second-line therapy in patients unable to tolerate rifampin during the continuation phase.

Don’t Forget!

Want an easy way to remember that ethambutol causes optic toxicity? Just remember: For ethambutol, the eyes have it!

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PART 4

ANTIFUNGAL DRUGS

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28 ANTIFUNGAL DRUGS

INTRODUCTION TO ANTIFUNGAL DRUGS

Fungi rule their own kingdom. There are possibly millions of species of these saprophytic and parasitic organisms, but, as with bacteria, only a small minority are human pathogens. Most pathogenic fungi are opportunistic and require a compromised host or disrupted anatomical barrier in order to cause infection in humans. In a way, the increase of systemic fungal infections can be seen as a marker of medicine's advance, because improvements in transplantation, oncology, rheumatology, neonatology, geriatrics, and other fields have created more susceptible hosts for fungi. The practice of medical mycology has expanded greatly.

Microscopic fungi exist in two basic forms: yeasts and molds. **TABLE 28-1** highlights some of the medically important fungi. Yeasts are unicellular forms of fungi that reproduce by budding. When they are left to grow in colonies, yeasts have a moist, shiny appearance. Molds are multicellular fungi that consist of many branching hyphae and can reproduce either by translocation of existing hyphae to a new area, or through spore formation and spread (hence, one bad apple really does spoil a bunch). They have a familiar fuzzy appearance, such as the *Rhizopus* that you have undoubtedly seen on bread.

TABLE 28-1 Fungi of Primary Clinical Concern

Yeasts	Dimorphic Fungi	Molds

Candida	Histoplasma	Aspergillus
Cryptococcus	Blastomyces	Fusarium
	Coccidioides	Scedosporium
	Sporothrix	Mucorales

In addition to these two basic forms, there are dimorphic fungi that can exist in either form. These fungi are often mold-like at room temperature but yeast-like at body temperature. They are frequently referred to as *endemic fungi* because many cause infections primarily within a certain geographic region; for example, *Coccidioides immitis* causes infections in the southwestern United States and central California, locally known as *valley fever*.

Yeasts, particularly *Candida* species, have become a leading cause of nosocomial bloodstream infections. Unfortunately, invasive *Candida* infections are challenging to diagnose: The presence of *Candida* in a culture might represent colonization, not infection (think colonization of urinary catheters). On the other hand, deep-seated *Candida* infections (such as hepatosplenic candidiasis) frequently are not detected by standard methods and sometimes only found on autopsy. Molds cause invasive disease primarily in immunocompromised hosts, but they should be considered in patients with various levels of immune system suppression, not just those in the most severe categories. Dimorphic fungi usually cause mild, self-limited disease, but some can also cause fatal disseminated disease, particularly in patients with suppressed immunity.

Antifungal pharmacotherapy has several challenges that often make fungal infections more difficult to treat than bacterial infections. One is that pathogens can be more difficult to isolate on culture than bacterial organisms. This makes the prompt initiation of empiric therapy important when invasive fungal infections are suspected. Prophylaxis may also be used in highly susceptible populations to prevent fungal infections from developing.

Another concern in the treatment of fungal disease is that many centers do not conduct antifungal susceptibility testing on clinical isolates. This forces clinicians to guess at likely susceptibility patterns based on speciation rather than test results. Even when susceptibility testing can suggest the “right” antifungal, the capabilities of the host significantly affect the likelihood of success in treating an invasive fungal infection. For neutropenic patients with mycoses, neutrophil recovery is a significant predictor of success, and patients with a prolonged immunocompromised status have a much worse prognosis. Therefore, while the selection of an appropriate antifungal is important, control of patient-specific factors is equally important to increase the likelihood of success, whether it is the need to remove a central venous catheter or to decrease doses of immunosuppressants.

Compared with the abundance of drugs available to kill bacteria, the number of systemic antifungal drugs is much lower. Selective toxicity is more difficult to achieve with eukaryotic fungi than with prokaryotic bacteria. Several newly marketed agents have changed the way fungal infections are treated. The chapters that follow introduce these agents in more detail.

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29
POLYENES

Agents: *amphotericin B, lipid formulations of amphotericin B*, nystatin (topical)

For many years, amphotericin B deoxycholate was the standard of care for many systemic fungal infections, based on both its broad antifungal spectrum and a lack of available alternatives. However, amphotericin B is notable for its toxicities, principally nephrotoxicity and infusion-related reactions. To attenuate these toxicities, three lipid-associated forms were developed: amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), and liposomal amphotericin B (LAmB). ABCD is no longer available.

Amphotericin B formulations have seen considerably less use since the introduction of the echinocandins and broad-spectrum azoles, but they still have utility. Activity against yeasts and many molds, proven efficacy in understudied disease states, and a long history of clinical experience help maintain their place in the antifungal armamentarium.

Mechanism of Action

Polyenes such as amphotericin B and nystatin bind to ergosterol in the fungal cell membrane, disrupting the fungal cell membrane and leading to the leakage of cell contents with eventual cell death.

Spectrum

Good: Most species of *Candida* and *Aspergillus*, *Cryptococcus neoformans*, dimorphic fungi, many molds

Moderate: Mucorales, *Fusarium, Scedosporium*

Poor: Candida lusitaniae, Aspergillus terreus, Lomentaspora

Adverse Effects

Infusion-related reactions: Infusion-related reactions with amphotericin B products include fever, chills, and rigors and can be treatment-limiting. These symptoms can be attenuated by premedicating with acetaminophen, hydrocortisone, and sometimes other medications. Liposomal amphotericin B has the lowest incidence of infusion-related reactions.

Renal: Nephrotoxicity with amphotericin B products is common. Both direct effects on the distal tubule and indirect effects through vasoconstriction of the afferent arteriole cause the nephrotoxicity, and nephrotoxicity also leads to wasting of magnesium and potassium, such that patients frequently need supplementation of these electrolytes. The lipid formulations have less nephrotoxicity than the conventional amphotericin B deoxycholate formulation; liposomal amphotericin B has the least.

Others: Increased transaminases and rash can occur with amphotericin B products as well.

Dosing Issues

The multiple formulations of amphotericin B can lead to confusion over their dosing. Amphotericin B deoxycholate is generally dosed between 0.5 and 1.5 mg/kg/d, where the lipid formulations are dosed at 3–6 mg/kg/d. Whether the lipid formulations are clinically equivalent with each other is a matter of debate, but most clinicians dose them as though they are. Fatal overdoses of amphotericin B deoxycholate have occurred when dosed as the lipid forms—a 3-5-fold overdose. Mind your formulation.

IMPORTANT FACTS

- Amphotericin B nephrotoxicity can be attenuated by the process of sodium loading: Administer boluses of normal saline before and after the amphotericin infusion. Sodium loading is an inexpensive and easy way of reducing risk to the kidneys if the patient's fluid status allows it.
- Many practitioners administer drugs such as acetaminophen, diphenhydramine, and hydrocortisone to decrease the incidence and severity of infusion-related reactions of amphotericin B. Meperidine is often given to treat rigors when they develop, but be wary of

using this drug in patients who develop renal dysfunction, because it has a neurotoxic metabolite that is eliminated renally.

- Whether differences in efficacy exist between the lipid formulations of amphotericin B is a matter of debate, but differences in safety do exist. In terms both infusion-related and nephrotoxic reactions, amphotericin B deoxycholate has the worst, whereas LAmB has the least.
- Nystatin is used only topically (as a cream for skin infections or an oral “swish and swallow” solution for thrush) due to poor tolerance when given systemically.

What They’re Good For

Amphotericin B formulations remain the drugs of choice for cryptococcal meningitis and serious forms of some other fungal infections, such as those caused by dimorphic fungi and some molds. Because of their broad spectrum, they are also a reasonable choice if fungal infection is suspected but the infecting organism is not known, as in febrile neutropenia. Their use in candidiasis and aspergillosis has declined with the availability of newer, safer, and more effective agents.

Don’t Forget!

Double-check that dose of amphotericin B. Which formulation are you using?

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ANTIFUNGAL ANTIMETABOLITE

Agent: flucytosine

Flucytosine (5-FC) was originally investigated as an oncology drug, but it was found to be significantly more active against fungi than against human cancer cells. The primary role of flucytosine is in combination therapy with amphotericin B formulations for cryptococcal disease. Because of its toxicity and low barrier for resistance when used as monotherapy, it is rarely used for other infections.

Mechanism of Action

Flucytosine is deaminated inside fungal cells to 5-fluorouracil (5-FU—yes, the cancer chemotherapy drug), which is further converted into metabolites that interfere with both protein and DNA synthesis. Fungi that do not express cytosine deaminase are not susceptible to flucytosine.

Spectrum

Good: Cryptococcus neoformans (used in combination with amphotericin B or fluconazole)

Moderate: Most species of *Candida*, *Aspergillus*

Poor: Many molds, *Candida krusei*

Adverse Effects

Conversion of flucytosine to 5-FU may occur outside fungal cells, potentially via gut microflora, and expose patients to side effects similar to those of this cytotoxic chemotherapy agent. Bone marrow suppression is the primary adverse effect of concern, particularly in higher doses or during prolonged courses. Hepatotoxicity is another adverse effect to be cautious of. Gastrointestinal complaints are more common, but they are less severe.

IMPORTANT FACTS

- Drug concentration monitoring is available for flucytosine: Check a peak concentration about 2 hours after the dose is given. However, do not rely on flucytosine concentrations alone to monitor for toxicity—hematology values are more important and more quickly available than drug levels. In most hospitals flucytosine levels are a "sendout" lab that can take up to a week to be resulted; given that the most common duration of therapy for flucytosine is 2 weeks, the practical utility of flucytosine levels may be limited.
- As with the rifamycin antimycobacterials, emergence of resistance during the course of therapy when used as monotherapy is a particular concern. In most cases flucytosine should be used as part of a combination regimen—if you see a patient on flucytosine, look for its "buddy."
- The most common use for flucytosine is in combination with an amphotericin B formulation for cryptococcal meningitis. Some studies, primarily in resource-limited settings, also report value in the combination of fluconazole and flucytosine, or amphotericin B and fluconazole.
- Flucytosine is commonly abbreviated as 5-FC, but this practice should be avoided because it can be confused with 5-FU.

What It's Good For

As previously stated, most flucytosine use is in combination with an amphotericin B formulation for treatment of cryptococcal meningitis. Successful use has been described with flucytosine monotherapy of *Candida* lower urinary tract infection when azoles are not an option due to allergy or resistance. Amphotericin and flucytosine given in combination are an option for treatment of *Candida* endocarditis (for which valve replacement surgery is the most important intervention).

Don't Forget!

Follow your patient's cell counts closely and consider dose modification or discontinuation if hematologic toxicity develops.

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31
AZOLES

INTRODUCTION TO AZOLES

Agents: *fluconazole*, itraconazole, *voriconazole*, *posaconazole*, *isavuconazole*, ketoconazole, multiple topical formulations and minor variants

The azoles are the workhorse class of antifungal agents, used for fungal infections ranging from minor to life-threatening. They target the ergosterol component of the fungal cell membrane, but instead of binding to ergosterol like the polyenes, azoles inhibit ergosterol production. This is achieved through inhibition of cytochrome P450 enzymes—similar to the ones humans use in drug metabolism. Thus, the potential for drug–drug interactions with drugs metabolized by CYP enzymes is among the most significant concerns with systemically administered azole antifungals. Although many drug interactions can be successfully dealt with by dosage adjustment and/or monitoring, this is not universally true and serious outcomes can arise. Also, remember that any dose adjustments made while a patient is receiving an interacting drug need to be readjusted when the therapy with the interactor is finished.

In recent years, azoles of variable antifungal spectrums and toxicity profiles have been introduced. Thus, while they share mechanisms and propensities for drug interactions, it is important to know the individual characteristics of each drug. In particular, there are a variety of formulations of each agent that can have important differences with regards to administration

with food and antacids (**TABLE 31-1**). This chapter discusses the commonly used systemic agents individually.

TABLE 31-1 Considerations for Oral Administration of Azole Antifungals

Drug	Fluconazole tablets	Voriconazole tablets	Itraconazole			Posaconazole		Isavuconazole
			Regular capsules	SUBA-itraconazole capsules	Solution	Solution	Tablets	
Food	Administer with or without food	Administer on empty stomach (1 hour separate from food)	Administer with food	Administer with food	Administer on empty stomach (1 hour separate from food)	Administer with high-fat meal	Administer with food	Give with or without food
Antacids*	No effect	No effect	Avoid	Unclear, consider avoiding	No effect	Avoid	No effect	No effect
Proton-pump inhibitors	No effect	Increases voriconazole levels	Decreases itraconazole levels	Increases itraconazole levels	Unclear	Decreases posaconazole levels	No effect	No effect

*Histamine-2 receptor antagonists, cation-based antacids (calcium, magnesium, aluminum)

Description

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FLUCONAZOLE

The introduction of fluconazole in 1990 was a breakthrough in antifungal pharmacotherapy. Fluconazole is highly bioavailable, available in both oral and IV formulations, and active against many species of *Candida* and other yeasts. Prior to fluconazole's approval, clinicians were faced with the toxicity and inconvenience of amphotericin B for serious forms of candidiasis. Fluconazole has a low incidence of serious adverse reactions, converting from IV to oral therapy is simple, and there are no limitations with regards to food or antacid therapy (Table 31-1). Though a shift toward non-*albicans* species of *Candida* has affected the utility of fluconazole, it remains an important, frequently utilized agent. The primary limitation to fluconazole's use is its lack of activity against molds such as *Aspergillus*.

Mechanism of Action

All azoles inhibit fungal cytochrome P450 14-alpha demethylase, inhibiting the conversion of lanosterol into ergosterol, which is a component of the fungal cell membrane.

Spectrum

Good: Candida albicans, Candida tropicalis, Candida parapsilosis, Candida lusitaniae, Cryptococcus neoformans, Coccidioides immitis

Moderate: Candida glabrata (can be susceptible dose-dependent, or resistant)

Poor: Molds, many dimorphic fungi, *Candida krusei, Candida auris*

Adverse Effects

Though fluconazole is generally well tolerated, hepatotoxicity is a concern and should be monitored for courses longer than a few days. As with all azoles, interactions with many drugs metabolized by the cytochrome P450 system are possible. Prolongation of the corrected QT interval (QTc) can be seen, and patients with risk factors for cardiac arrhythmias may require ECG monitoring.

Dosing Issues

Fluconazole doses for systemic fungal infections may be escalated, particularly for the treatment of *C glabrata* or *Coccidioides* infections. Be sure to adjust dosing with regard to renal function, because the drug has a significant component of renal elimination (unlike other azoles). Vulvovaginal candidiasis requires only a one-time dose of 150 mg of fluconazole.

IMPORTANT FACTS

- Fluconazole has no activity against *C krusei,* rare activity against *C auris*, and variable activity against *C glabrata*. Use against *C glabrata* should generally be only when fluconazole susceptibility has been documented, and can require doses of 800 mg/day of fluconazole after a loading dose. If your lab does not do susceptibility testing of fungi, consider an alternative agent such as an echinocandin.
- Fluconazole is often given as prophylaxis against *Candida* infections in susceptible populations like intensive care unit patients or patients with some cancers. Are you treating a patient who was receiving fluconazole prophylaxis and now has yeast in the blood? Try an echinocandin instead (since they may have fluconazole-resistant *Candida*). Even species of *Candida* that are normally susceptible to fluconazole (e.g., *C albicans*) can be resistant if the patient has recently received extended fluconazole prophylaxis.
- The high bioavailability of fluconazole (1:1 IV:po dosing) makes it an excellent therapy to transition to as patients tolerate oral medications.

What It’s Good For

Fluconazole remains a drug of choice for many susceptible fungal infections, including invasive and noninvasive candidiasis and cryptococcal disease. It is also used for some dimorphic fungal infections, such as coccidioidomycosis.

Don’t Forget!

Not all species of *Candida* are fluconazole-susceptible. Ensure that you check your patient’s isolate before committing to a definitive course of therapy with it.

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ITRACONAZOLE

Itraconazole is an in-between agent, with a broader spectrum than fluconazole but narrower than voriconazole, posaconazole, and isavuconazole. In addition, pharmacokinetic issues make it more complicated to use than other agents. Its current niche is primarily in the treatment of endemic (dimorphic) fungal infections.

Mechanism of Action

All azoles inhibit fungal cytochrome P450 14-alpha demethylase, inhibiting the conversion of lanosterol into ergosterol, which is a component of the fungal cell membrane.

Spectrum

Good: Dimorphic fungi including *Blastomyces*, *Histoplasma*, *Coccidioides*, and *Sporothrix*.

Moderate: Most *Candida* spp, *Aspergillus*

Poor: Mucorales, many other molds

Adverse Effects

Itraconazole's adverse effect profile causes more concerns than that of fluconazole. In addition to causing hepatotoxicity and QTc prolongation, itraconazole is a negative inotrope and is contraindicated in patients with heart failure. The oral solution is associated with diarrhea. It is also a potent inhibitor of cytochrome P450 enzymes and has a long list of drug interactions.

IMPORTANT FACTS

- Itraconazole comes in three different formulations with different bioavailabilities and requirements (Table 31-1). The oral formulations of itraconazole have different instructions with regard to taking them with meals. The capsule formulations (regular and “SUBA” [SUper BioAvailability]) should always be taken with a full meal, whereas the solution should be taken on an empty stomach. The effect of acid-reducing agents varies as well: Regular capsules should be avoided with any sort of acid-reducing agent because absorption is impaired, whereas the SUBA capsules may have their levels increased by proton-pump inhibitors. The bottom line is, these formulations are not directly interchangeable, so close attention needs to be paid to which formulation your patient is taking—insurance companies may authorize one formulation and not another, leading to errors if attention is not paid.
- Because itraconazole absorption is so erratic and unpredictable, concentrations are often monitored. Consider checking a trough concentration on your patient if he or she is taking it for a serious fungal infection and/or for a long time.
- Itraconazole was once available in an IV formulation, but this has been discontinued by the manufacturer. Ignore less-sophisticated references that suggest using it.

What It’s Good For

Itraconazole remains a drug of choice for some dimorphic fungal infections, like histoplasmosis. It once had a larger role in the management and prophylaxis of aspergillosis and other mold infections, but it has been largely replaced by newer azoles with better pharmacokinetics. Itraconazole capsules are also used for the treatment of onychomycosis.

Don’t Forget!

EXACTLY which formulation of itraconazole is your patient taking again?

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VORICONAZOLE

The introduction of voriconazole represented a significant improvement in the treatment of mold infections. It is a broad-spectrum antifungal like itraconazole, with good activity against *Candida* species and many molds. Unlike itraconazole, voriconazole is well absorbed and available in both highly bioavailable oral formulations and an IV preparation. Most importantly, voriconazole is a drug of choice for invasive aspergillosis. With voriconazole's widespread use, however, limitations in terms of highly variable pharmacokinetics and long-term adverse effects have emerged.

Mechanism of Action

All azoles inhibit fungal cytochrome P450 14-alpha demethylase, inhibiting the conversion of lanosterol into ergosterol, which is a component of the fungal cell membrane.

Spectrum

Good: C albicans, C lusitaniae, C parapsilosis, C tropicalis, C krusei, C neoformans, Aspergillus species, many other molds

Moderate: C glabrata, C albicans that are fluconazole-resistant, *Fusarium* species

Poor: Mucorales

Adverse Effects

In addition to the hepatotoxicity, rash, and drug interactions that are common with this class,

voriconazole has some agent-specific adverse effects worth watching.

Renal: The cyclodextrin solubilizer that intravenous voriconazole comes in is known to accumulate in renal dysfunction. This vehicle is thought to be nephrotoxic, but it is almost certainly less nephrotoxic that amphotericin B, so the use of intravenous voriconazole with renally insufficient patients is a risk/reward equation that should be considered with each patient. Studies suggest that tolerance of the vehicle is good, especially with short durations of therapy.

Visual effects: Visual effects such as seeing wavy lines or halos around bright lights are very common and dose-related; they tend to go away with continued use and are most common with the loading doses.

Central nervous system effects: Distinct from the common visual effects of voriconazole, patients sometimes experience visual and auditory hallucinations. These effects are not permanent and tend to occur at higher voriconazole levels (especially during peak concentration periods).

Dermatologic: Voriconazole has long been known to cause sun sensitivity, and patients should be advised to use sunscreen and avoid excessive sun exposure. Because voriconazole has been shown to be so useful for treating and preventing fungal infections, it has been used for durations far exceeding those studied in clinical trials. However, some studies now suggest an association between prolonged voriconazole use and certain skin cancers. Thus, it is even more essential to counsel patients on reducing sun exposure if they are taking voriconazole.

Dosing Issues

Voriconazole has highly variable interpatient pharmacokinetics and nonlinear elimination, making it difficult to dose correctly. If you are committing your patient to an extended course of therapy for voriconazole, the standard of care has become to monitor serum drug concentrations (usually a trough level). There is no official consensus, but trough concentrations in the range of 2–5 mg/L are usually considered to be in the therapeutic window.

IMPORTANT FACTS

- Voriconazole is active against some fluconazole-resistant strains of *C albicans*, but it is less active against them than fluconazole-susceptible strains. An echinocandin is a better choice, if you need to use voriconazole for an oral option against any fluconazole-resistant *Candida* (other than *C krusei)* than susceptibility testing is essential.
- Voriconazole is a potent inhibitor and a substrate of the cytochrome P450 system. The list

of drugs that interact with voriconazole is long and varied. Some of them, such as rifampin, are contraindicated, whereas others, such as calcineurin inhibitors (e.g., cyclosporine), require dose adjustments. This is significant because many of the patients who require voriconazole are immunosuppressed.

- Voriconazole is eliminated hepatically and is unlikely to be useful in the treatment of candiduria, so don't reach for voriconazole if your patient has a fluconazole-resistant *Candida* UTI.

What It's Good For

Voriconazole is a drug of choice for invasive aspergillosis and is frequently used in the treatment of infections caused by other molds. It can be used for candidiasis as well, but fluconazole and echinocandins are more frequently used for these infections. Some clinicians use voriconazole in the empiric treatment of febrile neutropenia and in prophylaxis against mold infections in immunocompromised patients.

Don't Forget!

Watch for drug interactions with voriconazole, and consider checking drug concentrations if you are using it for an extended course of therapy.

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POSACONAZOLE

Posaconazole is an analog of itraconazole that is substantially more active against many fungi. It was the first azole with good activity against *Mucorales,* a difficult-to-treat order of molds that most antifungals (voriconazole included) do not treat; however, the recently approved isavuconazole also has activity against these pathogens (see the next section). Recently posaconazole was shown to be noninferior to voriconazole in the treatment of invasive aspergillosis.

Mechanism of Action

All azoles inhibit fungal cytochrome P450 14-alpha demethylase, inhibiting the conversion of lanosterol into ergosterol, which is a component of the fungal cell membrane.

Spectrum

Good: Aspergillus species, *Mucorales*, many other molds, dimorphic fungi, most *Candida* spp

Moderate: Fusarium species, *C glabrata*

Adverse Reactions

Posaconazole carries similar risks of hepatotoxicity and QT prolongation as other azoles but lacks the sensory or cutaneous side effects of voriconazole. While it is a perpetrator of drug interactions via its strong inhibition of CYP 3A4, it is not a CYP substrate itself and so is slightly

less likely to be a drug interaction problem. However, its inhibition of enzymes involved in steroid metabolism has led to cases of hypertension and hypokalemia as a component of posaconazole-induced pseudohyperaldosteronism.

Dosing Issues

As with itraconazole, there are multiple oral preparations with important differences between them. The oral suspension formulation was the first FDA-approved preparation and requires administration with food to increase its absorption (Table 31-1); foods with a high fat concentration, nutritional supplements containing fat, and low-pH beverages like soda all increase absorption. Even under the best circumstances, absorption of the suspension is limited and variable. Subsequently a delayed-release tablet formulation has been approved that achieves much higher and more reliable concentrations. There is also an IV formulation that contains a cyclodextrin solubilizer; as with the IV voriconazole preparation, administration of the IV form to patients with renal failure is a risk/benefit decision (which almost always comes down in favor of giving the IV posaconazole).

IMPORTANT FACTS

- Posaconazole's most common use has been in the prophylaxis of fungal infections in high-risk patients. As with voriconazole, many of these patients are taking immunosuppressants that interact with posaconazole, so keep close tabs on those drug concentrations.
- The *in vitro* activity of posaconazole against *Aspergillus* is generally similar to that of voriconazole. Previously, a lack of clinical trial data comparing posaconazole to voriconazole relegated it to second-line use, but with the publication of recent study showing similar outcomes in invasive aspergillosis, posaconazole may become a first-line agent.
- Although its pharmacokinetics are less variable than voriconazole's, assays for posaconazole drug concentrations are available and their measurement should be considered for patients with questionable absorption, or if posaconazole is being used for treatment of invasive infections.

What It's Good For

Posaconazole is most commonly used as prophylaxis against fungal infections in susceptible hosts, but it also plays a key role in the management of mucormycosis and may see increasing use in treatment of invasive aspergillosis. It is used as an alternative in oropharyngeal candidiasis and fungal infections refractory to other agents.

Don't Forget!

As with itraconazole, it is vitally important to take into account which formulation your patient is

taking and dose and administer accordingly.

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ISAVUCONAZOLE

The newest azole antifungal is isavuconazole. In many ways isavuconazole is similar to posaconazole. It has an expanded spectrum of activity that includes *Candida*, *Aspergillus*, and Mucorales. It is available as IV and oral formulations, has P450-mediated drug interactions, and a toxicity profile that is most concerning for hepatic effects.

Mechanism of Action

All azoles inhibit fungal cytochrome P450 14-alpha demethylase, inhibiting the conversion of lanosterol into ergosterol, which is a component of the fungal cell membrane.

Spectrum

Good: Candida spp (see the upcoming section “Important Facts” regarding clinical trial data about isavuconazole in invasive candidiasis), *Aspergillus* species, *Mucorales*, some other molds and dimorphic fungi

Moderate: C glabrata

Poor: Fusarium species

Adverse Reactions

Based on clinical trial data, hepatotoxicity on a similar level to other azole antifungals is anticipated (although it may be somewhat less frequent than with voriconazole). Interestingly,

unlike other azoles, isavuconazole does not appear to prolong the QT interval but can actually shorten it. This does not seem to have clinical significance besides among patients with congenitally short QT intervals, and may allow for use of isavuconazole in patients with prolonged QT intervals who would be at risk of an arrhythmia if prescribed a different azole antifungal. The sensory effects of voriconazole and the pseudohypoaldosteronism of posaconazole have not been described with isavuconazole.

Dosing Issues

The bioavailability of isavuconazole's oral formulation (a capsule) is excellent and not affected by food or gastric acidity. However, the capsules are not designed to be opened, crushed, or chewed, which limits their administration among patients with feeding tubes or swallowing issues. (Studies of opening and administering the capsules, or just having patients swallow the IV formulation, are in progress.) Isavuconazole has a very long half-life, so to attain therapeutic levels more rapidly, there is an extensive loading dose regimen: administration every 8 hours for 6 doses (48 hours), before transition to a once-daily maintenance regimen. Isavuconazole is supplied as a prodrug (isavucazonium sulfate) that is hydrolyzed to isavuconazole after administration; however, this makes for funky dosing: 372 mg of isavucazonium yields 200 mg of isavuconazole. This leads to the potential for confusion in ordering doses. Be sure to verify any dosing that looks unfamiliar.

IMPORTANT FACTS

- Isavuconazole has *in vitro* activity against *Candida* species that appears to be similar to that of voriconazole and posaconazole. A phase III randomized clinical trial was performed against caspofungin among patients with invasive *Candida* infections. The conclusion of this study was that isavuconazole was not noninferior to caspofungin in the treatment of these infections—the FDA is not going to be granting isavuconazole an indication for invasive candidiasis. However, whether or not isavuconazole is a worse option than voriconazole or posaconazole for these infections is a matter of debate. Posaconazole has FDA approval for only the less-severe oropharyngeal candidiasis and has not been studied in clinical trials for invasive candidiasis. Voriconazole is FDA approved for invasive candidiasis based on the results of a study comparing it to conventional amphotericin B followed by fluconazole. Subsequent studies have suggested that echinocandins may be more effective than both amphotericin and fluconazole in treatment of invasive *Candida* infections. Thus, isavuconazole may have suffered the misfortune of being compared against the most effective anti-*Candida* agent (echinocandins), whereas voriconazole got to "play against the JV team," and posaconazole was not even studied. The bottom line: For invasive candidiasis, whenever possible use an echinocandin (most effective) or fluconazole (balance of efficacy and convenience).

- Isavuconazole's pharmacokinetics is more predictable than voriconazole's and possibly posaconazole's; however, clinicians are frequently reassured by demonstrating adequate serum drug levels. Currently, fewer laboratories offer isavuconazole levels than voriconazole or posaconazole levels, but this is likely to increase over time.

What It's Good For

Isavuconazole is primarily used for the treatment of invasive mold infections, either *Mucorales* or *Aspergillus*.

Don't Forget!

Double-check that dosing—it's important to give the correct dose as well as the full loading regimen; otherwise, your patient will take a week to get to a subtherapeutic steady-state.

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ECHINOCANDINS

Agents: *caspofungin, micafungin, anidulafungin*

The echinocandins and their new sister class, the terpenoids (discussed in Chapter 33), exploit a different structural target than other antifungal classes: the fungal cell wall. The three available echinocandins are similar drugs with virtually indistinguishable spectra. They are very well tolerated and have excellent activity against *Candida* and useful activity against some other fungi, but they all suffer from the same pharmacokinetic setback: lack of an oral formulation. They have considerably fewer drug interactions than azoles, are safer than polyenes, and have great activity against fluconazole-resistant yeasts.

Mechanism of Action

Echinocandins inhibit beta-1,3-D-glucan synthase, the enzyme responsible for the production of beta-1,3-D-glucan, a vital component of the cell wall of many fungi.

Spectrum

Good: Candida albicans, Candida glabrata, Candida lusitaniae, Candida parapsilosis, Candida tropicalis, Candida krusei

Moderate: Aspergillus species, some dimorphic fungi, *Candida auris*

Poor: Most non-*Aspergillus* molds, *Cryptococcus neoformans,* some weird yeasts (e.g., *Trichosporon*)

Adverse Effects

Echinocandins have an excellent safety profile. They can cause mild histamine-mediated infusion-related reactions, but these are not common and can be ameliorated by slowing the infusion rate. Hepatotoxicity is also possible with any of these agents, but this is not commonly seen and occurs less frequently than with most azoles.

IMPORTANT FACTS

- Differences among the echinocandins are minor and mostly pharmacokinetic. Caspofungin and micafungin are eliminated hepatically by noncytochrome P450 metabolism, whereas anidulafungin degrades in the plasma and avoids hepatic metabolism. Despite this unique method of elimination, anidulafungin is not completely devoid of hepatotoxicity.
- Echinocandins have excellent fungicidal activity against *Candida*, but against *Aspergillus* species they exhibit activity that is neither classically cidal nor static. Instead, they cause aberrant, nonfunctional hyphae to be formed by the actively growing mold.
- The echinocandins are only modestly active against molds but appear to substantially enhance the effects of other antifungals against these pathogens. A randomized controlled trial of voriconazole with or without anidulafungin in invasive aspergillosis showed a trend toward reduced mortality among patients receiving combination therapy. (The difference was not statistically significant—p = 0.07—but given the low toxicity of echinocandins, many clinicians refuse to submit to the tyranny of the p-value and advocate for the use of this combination therapy). The echinocandins may also enhance the efficacy of liposomal amphotericin B against *Mucorales* infections, based on *in vitro* and limited clinical data.
- Though drug interactions with the echinocandins are minor, you should be aware of some of them, particularly with caspofungin and micafungin. Be careful when you use them with the immunosuppressants cyclosporine (caspofungin) and sirolimus (micafungin).

What They’re Good For

Echinocandins are drugs of choice for invasive candidiasis, based on head-to-head randomized trials and real-world cohort studies. They are particularly important as initial therapy in patients who are clinically unstable or if there is a risk the infection is caused by an azole-resistant species; if susceptibility to azoles is confirmed, it is reasonable to complete therapy with an azole after the patient stabilizes (mostly to allow for transition to oral therapy). Echinocandins are also an alternative in the treatment of invasive aspergillosis but do not have the level of supporting data that voriconazole and the polyenes do for this indication. All of the

echinocandins are used for esophageal candidiasis, and some are used in prophylaxis or empiric therapy of fungal infections in neutropenic patients. Some clinicians will add an echinocandin to voriconazole (for *Aspergillus* infections) or an amphotericin B formulation (versus *Mucorales*) in an attempt to increase likelihood of cure for these infections.

Don’t Forget!

A report of “yeast in the blood” should have you reaching for an echinocandin—as long as you pause for a moment to consider the likelihood of other yeasts such as *Cryptococcus* in your specific patient first. Those are pretty rare; but don’t forget that they can occur.

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33 TERPENOIDS

Agents: ibrexafungerp

Welcome to our new friend with the funny name (eye-BREX-ah-FUN-jerp), first in class of the terpenoids (or "-fungerps" if you prefer). These agents inhibit beta-1,3-D-glucan synthase, the same target as the echinocandins, but are structurally distinct from the echinocandins. Although they bind to the same target enzyme, cross-resistance is not complete and ibrexafungerp may have utility against some echinocandin-resistant isolates. Ibrexafungerp also displays reasonable oral bioavailability, unlike the echinocandins. Ibrexafungerp was only recently approved for the treatment of vulvovaginal candidiasis (VVC) in women, and it may have a role in practice for invasive fungal infections; we await the results of clinical trials in invasive disease.

Mechanism of Action

Ibrexafungerp inhibits beta-1,3-D-glucan synthase, the enzyme responsible for the production of beta-1,3-D-glucan, via a similar but not identical mechanism to the echinocandins.

Spectrum

Good: Candida spp

Moderate: Aspergillus species, some dimorphic fungi

Adverse Effects

Little data is available to date on adverse effects of ibrexafungerp. In early clinical trials, gastrointestinal adverse effects were the primary toxicity noted. VVC trials used only 2 doses of medications, so other adverse effects may be seen with prolonged dosing in different indications.

IMPORTANT FACTS

- Ibrexafungerp was FDA-approved for treatment of VVC as a one-day, two-dose regimen. Different doses and durations are under study for invasive infections.
- A potential downside of ibrexafungerp relative to echinocandins may be a greater potential for drug interactions, as ibrexafungerp appears to inhibit P450 enzymes and is a substrate of CYP 3A4.

What They’re Good For

Well, right now ibrexafungerp is approved only for vulvovaginal candidiasis (a condition for which many other topical and oral antifungal therapies are available). As more data accumulates, however, the hope is this class will be an alternative oral option for treatment of all manner of *Candida* infections.

Don’t Forget!

It’s not an “oral echinocandin.” Well, it sort of is, but there are important differences, especially with regard to potential drug interactions.

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PART 5

ANTIVIRAL DRUGS

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ANTIVIRAL DRUGS

INTRODUCTION TO ANTIVIRAL DRUGS

The term *virus* has interesting meanings in popular culture: It is commonly used to describe something that has or can spread quickly from person to person, such as a computer virus or a “viral” video (a video that gains quick popularity through social media). This usage represents a basic understanding of the high transmissibility of many respiratory viruses, such as the influenza virus and coronaviruses. Obviously the COVID-19 pandemic (caused by the SARS-CoV-2 coronavirus) has been a stark illustration of how quickly and widely a virus can spread. However, many less-well-understood viruses, particularly those that cause chronic disease, can be confusing in their transmission and life cycle.

The world of viruses is very different from that of prokaryotes and eukaryotes. Viruses are dependent on cells to replicate and cannot perpetuate without them. They are considerably smaller than eukaryotes and even much smaller than most prokaryotes, though they vary widely in size (see Figure 1.2). They are relatively simple organisms compared with prokaryotes or eukaryotes, but they outnumber all other forms of life on earth. Scientists have debated for many years about whether viruses are life forms or not, and no clear consensus yet exists. The understanding of how they interact with and shape the existence of living cells, however, has increased greatly since they were described by Louis Pasteur in the late nineteenth century.

An in-depth discussion of the structure of viruses is beyond the scope of this text, but a basic understanding of viruses will help you understand the actions of antiviral drugs. Viruses are highly diverse, though nearly all of them share a few common characteristics. Many are

covered by a viral *envelope* as their outmost layer, composed of elements of the host cell membrane, endoplasmic reticulum, or nuclear envelope. This layer covers the *capsid*, a shell composed of identical building blocks of *capsomeres*. The capsid protects the viral *nucleic acid*, which is either DNA or RNA but not both (as in cells). The DNA or RNA can be either single- or double-stranded. Finally, many viruses contain enzymes that catalyze reactions that lead to their replication or cell entry. Viruses cannot synthesize their own components to replicate—they are dependent on host cellular processes for all synthetic functions. Individual complete particles of virus are termed *virions*.

The specific steps of the viral life cycle differ from virus to virus, but they follow the same basic pathway. Viruses spread from host to host through various means—some through direct inhalation, some through direct fluid exchange, some through vectors such as mosquitoes. Once a virus reaches its target cell, it has to penetrate the cell membrane. Specific receptors on the cell and viral surfaces facilitate this process. The virus then uncoats and releases its genetic information from the capsule into the host cell. The host cell reads the genetic material and translates it into viral proteins. How exactly this proceeds depends on the form in which the genetic material exists in the virus. In some cases, the genetic material is encoded as RNA. For some RNA viruses, host cell ribosomes translate the RNA into proteins. In the group of viruses known as retroviruses, the RNA genetic material is first translated into DNA (via an enzyme known as *reverse transcriptase*) before integrating into the host genome. For these viruses or those viruses whose genome is already encoded as DNA, transcription into messenger RNA occurs, followed by translation into protein. Once the pieces of the puzzle are built, the viral enzymes assemble them into complete virions, and they are finally released from the cell. The available antiviral drugs are aimed at various steps in this cycle.

The pharmacotherapy of viral infections is different from that of bacterial infections. Few antivirals are “broad-spectrum” in the sense we use for antibacterials; generally an antiviral is useful only against a particular virus or closely related viruses. Patient-specific viral susceptibility results are rarely available, leaving practitioners to choose therapies based on general patterns of susceptibility for that type of virus. (HIV is a notable exception, where susceptibility testing based on genotyping is a standard of care.) While viruses can be cultured, most viral illnesses are diagnosed through genetic testing for viral antigens or nucleic acids. These tests can be followed quantitatively to see if an infection improves, but for short-term infections symptoms are usually followed instead. Most common viral infections have no effective pharmacotherapeutic remedy, which is a fancy way of saying that there is still “no cure for the common cold.”

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ANTI-HERPES SIMPLEX VIRUS AND VARICELLA-ZOSTER VIRUS AGENTS

Agents: *acyclovir*, valacyclovir, famciclovir

These agents are primarily used in the treatment of infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV), though they are active against some other viruses as well. Acyclovir is poorly absorbed and must be given up to 5 times daily when administered orally; valacyclovir and famciclovir are prodrugs that are absorbed better and can be administered less frequently. Only acyclovir can be administered intravenously, and it is the agent of choice for serious HSV infections such as encephalitis.

Mechanism of Action

These drugs are nucleoside analogs that, after phosphorylation, are incorporated into the elongating viral DNA strand just like cellular nucleotides; however, they lack the functional group that allows the next nucleotide to be added, halting replication.

Spectrum

Good: HSV-1 and HSV-2

Moderate: VZV

Poor: Epstein-Barr virus (EBV), cytomegalovirus (CMV), HIV

Adverse Effects

These drugs are generally well tolerated with few adverse effects. The most concerning adverse effect is nephrotoxicity through either crystallization or acute interstitial nephritis (AIN), most commonly associated with IV acyclovir in higher doses. Crystallization is preventable through hydration and correct dosing in renally impaired patients. Seizures, tremors, or other central nervous system (CNS) effects can also occur. Nausea, diarrhea, and rash are more common. Thrombotic thrombocytopenic purpura has been reported with valacyclovir in HIV patients.

IMPORTANT FACTS

- Valacyclovir is a prodrug of acyclovir with substantially improved bioavailability and less-frequent dosing. Famciclovir is a prodrug of penciclovir, an agent that is available only as a topical preparation.
- Acyclovir dosing varies widely by indication and host status. Be sure to double-check that it is appropriate for your patients.
- Acyclovir is most nephrotoxic in combination with diuretics or other nephrotoxins. Keep your patients hydrated during acyclovir therapy, particularly if it is given in higher IV doses.

What They’re Good For

Intravenous acyclovir is the drug of choice for severe or difficult-to-treat HSV infections, such as encephalitis or severe HSV outbreaks among immunocompromised patients. Any of these agents can be used to treat genital herpes (usually caused by HSV-2) to decrease symptom duration and as prophylaxis if patients have frequent recurrences. They are all also effective in treating VZV infection, although VZV is intrinsically less susceptible, and thus higher doses are often necessary.

Don’t Forget!

Valacyclovir typically has much more patient-friendly dosing than acyclovir—unless their out of pocket cost will be significantly higher, patients will typically prefer valacyclovir!

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ANTI-CYTOMEGALOVIRUS AGENTS

Agents: *ganciclovir*, valganciclovir, *foscarnet, cidofovir*, letermovir

Cytomegalovirus (CMV) causes infections that are usually asymptomatic or mildly symptomatic in immunocompetent patients but can be devastating in immunocompromised patients. Approximately 60% of Americans become seropositive for CMV by adulthood, and like other herpesviruses, infection is lifelong and typically latent. If a patient becomes immunocompromised, the infection can reactivate and the patient may need pharmacotherapy. The anti-CMV agents discussed here work by preventing viral replication but at slightly different stages in the process. Historically all the agents have had significant and often-treatment-limiting toxicity; the newest agent, letermovir, has substantially less toxicity but does have other limitations.

Mechanisms of Action

Ganciclovir is a nucleoside analogue that, after phosphorylation, is integrated into viral DNA by DNA polymerase, halting viral replication. Valganciclovir is a prodrug of ganciclovir.

Cidofovir is a nucleotide analogue that has a similar mechanism to ganciclovir but does not require phosphorylation and can be active against some ganciclovir-resistant strains of viruses.

Foscarnet is a pyrophosphate analogue that acts as a noncompetitive inhibitor of the DNA and RNA polymerases of multiple viruses.

Letermovir inhibits later stages of viral replication, where the newly created viral DNA strands

are packaged into viral “shells.” The enzymes that perform this function are called *terminases*, and letermovir inhibits this step, preventing creation of intact virions.

Spectrum

Good: Ganciclovir, cidofovir, foscarnet: CMV, HSV-1, HSV-2, VZV

Letermovir: CMV

Moderate: Cidofovir: adenovirus, BK virus

Adverse Effects

Ganciclovir and valganciclovir are the same active drug and have the same adverse reactions. They both have dose-dependent myelosuppression that is relatively common, particularly when used in higher doses or in renally impaired patients without dose adjustment. Foscarnet is nephrotoxic and neurotoxic, and it is reserved for patients who are intolerant of or failed other therapy. Foscarnet can also cause profound electrolyte abnormalities. Cidofovir is an uncommonly used agent that also exhibits significant nephrotoxicity. Nausea, vomiting, and diarrhea can occur from any of these agents. Letermovir is much better tolerated, with an adverse effect profile similar to placebo in its main trial to date.

IMPORTANT FACTS

- ValGANciclovir and valAcyclovir are both prodrugs that improve bioavailability of their parent drugs, but it is important not to get them confused, as the parent drugs have important differences.
- Ganciclovir must be carefully dosed by patient weight and renal function. Monitor patients closely for changes in renal function when they are on therapy.
- The package insert for valganciclovir specifies dose adjustment for renal dysfunction but not weight. It comes in two strengths: 900 mg and 450 mg. The dose of 900 mg bid is considered to be equivalent to 5 mg/kg q12h of IV ganciclovir, but it may be much more than that for an underweight patient because it is approximately 60% bioavailable. Consider this example for a 50-kg patient:

  Ganciclovir dose = 50 kg × 5 mg/kg = 250 mg ganciclovir

  Valganciclovir dose = 900 mg × 0.60 bioavailability = 540 mg of active ganciclovir
- This patient would receive more than double the amount of active ganciclovir if 900 mg bid of valganciclovir were used. Consider very close monitoring and potential dose adjustment in underweight patients, particularly if they are at high risk of toxicity.
- The nephrotoxicity of foscarnet and cidofovir is such that both require extensive

prehydration regimens with normal saline to reduce the toxicity risk. Cidofovir actually requires coadministration with probenecid for most indications, which reduces the excretion of cidofovir into the renal tubules, prolongs its half-life, and attenuates its toxicity.

- Letermovir has significantly less toxicity than other anti-CMV agents, but it has an Achilles' heel: resistance can develop rapidly to this agent. In trials where letermovir was used for primary prophylaxis against CMV in immunocompromised patients, the rates of emergent resistance were fairly low, but in case reports of letermovir used for salvage therapy for CMV, emergence of resistance is common. For this reason, letermovir's primary role to date has been in prophylaxis where viral loads are lower and emergence of spontaneous mutants is less likely. Future trials will determine whether letermovir can play a significant role in treating active CMV disease. Note as well that letermovir does not provide activity against HSV or VZV, so patients using letermovir as prophylaxis may require adjunctive acyclovir.
- It takes a while, but genotype-based susceptibility testing is available for CMV and is usually performed if resistance is suspected in patients not responding to ganciclovir. The genotype will reveal whether ganciclovir resistance is present and whether cidofovir or foscarnet is a therapeutic option.

What They're Good For

Ganciclovir and valganciclovir are first-line drugs for the treatment and prevention of CMV infections. Valganciclovir is often given to prevent CMV infection after transplant. Foscarnet is a second-line agent for CMV that can also be used for severe or resistant HSV infections. Cidofovir is a second-line agent for CMV and a few other viral infections (adenovirus, BK virus)—given its toxicity it is typically only used for severe manifestations of those viruses, usually in immunocompromised hosts. Letermovir is used for prophylaxis against CMV infection in high-risk immunocompromised hosts.

Don't Forget!

Although valganciclovir is orally administered, it is has good bioavailability and has adverse effects identical to those of ganciclovir. Valganciclovir use requires monitoring for toxicity that is just as rigorous as that used for intravenous ganciclovir.

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ANTI-INFLUENZA ANTIVIRALS

Agents: oseltamivir, *peramivir*, zanamivir (inhaled), baloxavir

Two classes of agents are used clinically as anti-influenza antivirals. There are three neuraminidase inhibitors that differ in their forms of delivery: Oseltamivir is an oral prodrug, whereas peramivir is intravenous, and zanamivir is inhaled. They can be used in either the treatment of influenza or as prophylaxis for patients who cannot take the influenza vaccine. The newer class of endonuclease inhibitors, represented by baloxavir, is available only for oral administration and is approved for single-dose treatment or postexposure prophylaxis of influenza.

Mechanism of Action

The neuraminidase inhibitors are competitive inhibitors of viral neuraminidase, an enzyme responsible for several functions of the influenza virus, including the release of new virions from infected cells.

Endonuclease inhibitors target mRNA transcription and interrupt viral replication within the cell. Cross-resistance between the two classes of agents is not anticipated.

Spectrum

Good: Influenza A and B

Poor: Other viruses

Adverse Effects

All these agents are generally well tolerated. Oseltamivir can cause nausea, vomiting, and abdominal pain, but these tend to be transient effects. Headache and fatigue can also occur, particularly during prophylactic use when the drug is given for a longer period of time. Zanamivir has mostly pulmonary adverse effects, including cough and bronchospasm, possibly related to the excipients in the dry-powder formulation. Avoid using it in patients with asthma or other reactive pulmonary diseases. Peramivir doesn't seem to have any characteristic adverse effects based on limited experience to date. Baloxavir is very well tolerated with an incidence of adverse effects similar to placebo in clinical trials.

IMPORTANT FACTS

- Anti-influenza antivirals are most effective when started early in the course of infection, because viral replication peaks early (within 72 hours after infection). The package inserts for these drugs state they should be started in patients who have been symptomatic for no more than 2 days—this is based on the labeled indications for mild–moderate infection in healthy adults. In severe influenza infections—such as those that require hospitalization—or in vulnerable patients, data suggest there may be benefit even if therapy is delayed, so treatment guidelines recommend initiating treatment even if outside the "window" for these patients. (Notably, most of the data here are with oseltamivir.)
- Resistance to both classes of agents can occur, although resistance emerges independently. (There is not cross-resistance.) Neuraminidase inhibitors have a fairly high barrier to resistance; emergence of resistance among isolates initially susceptible tends to occur mostly in immunocompromised patients. Prior years have seen circulation of influenza strains with preexisting neuraminidase inhibitor resistance, but these have not been common recently. (Knock on wood!) Currently, zanamivir is active against the vast majority of oseltamivir- and peramivir-resistant strains, but these resistance patterns may change. Resistance to baloxavir is a different story, with a significant fraction of patients (up to 10%) harboring isolates with baloxavir resistance after exposure. Baloxavir-resistant isolates can be transmitted and seem to be associated with slower viral clearance relative to susceptible isolates.
- Oseltamivir and zanamivir are highly effective at preventing influenza infection when the predominant strains in the community are susceptible, but they are not substitutes for a vaccination strategy. Adverse effects are more common with the prolonged use seen with prophylactic use than with the shorter durations of therapeutic use. Baloxavir was also very

effective in preventing influenza infection as a single dose given to household contacts of influenza cases, but resistance is a concern with this use as well.

What They're Good For

All the neuraminidase inhibitors are effective at treating and preventing uncomplicated influenza infections if the circulating strains are susceptible (and when initiated as soon as possible after symptom onset). The vast majority of the data on use in more-severe disease is from observational studies with oseltamivir, so that agent is used preferentially among hospitalized and high-risk patients. Baloxavir is used single-dose therapy for uncomplicated influenza and as single-dose prophylaxis among household contacts of influenza cases.

Don't Forget!

If your patients are otherwise healthy and their flu has peaked and they are improving, then their window of benefit has likely closed; but if they are severely ill or have multiple comorbidities, consider antiviral therapy no matter how long it has been since the onset of symptoms.

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ANTI-CORONAVIRUS ANTIVIRALS

Agents: *remdesivir*, nirmatrelvir/ritonavir, molnupiravir

When the COVID-19 pandemic exploded across the world, scientists everywhere scrambled to test practically every drug in clinical use or in the near development pipeline for activity against SARS-CoV-2. An agent that had been studied in phase II trials for *Ebolavirus* infection and noted to have *in vitro* activity against the SARS-CoV and MERS coronaviruses, remdesivir was found to have potent activity versus SARS-CoV-2. Remdesivir has subsequently been studied in an alphabet soup of clinical trials for COVID (ACTT-1, RECOVERY, DisCoVeRy, PINETREE, etc.), ultimately being granted FDA approval but with lingering questions over its effectiveness and place in therapy. As of the time this book went to press, another agent (nirmatrelvir/ritonavir—brand name Paxlovid) has just gained Emergency Use Authorization (EUA) and another agent (molnupiravir) is under EUA review. These agents may already be an important part of treatment for COVID-19 by the time you read this.

Mechanism of Action

After intracellular metabolism of its prodrug form into the triphosphorylated nucleotide analog, remdesivir acts as a nucleotide analog inside infected cells, inhibiting viral RNA-dependent RNA polymerase.

Spectrum

Good: SARS-CoV-2, SARS-CoV*, MERS*

Moderate: Ebola virus, Marburg virus*, respiratory syncytial virus (RSV)*, hepatitis C virus (HCV)*

*Based on *in vitro*/animal model data

Adverse Effects

Remdesivir appears to be well tolerated overall. Elevations of hepatic transaminases can occur but typically only require holding the drug if they exceed 10 times the upper limit of normal. Like several other antimicrobials (voriconazole, posaconazole), the intravenous form of remdesivir contains a cyclodextrin solubilizer, which is cleared renally. Concern over accumulation of cyclodextrin and subsequent renal and hepatic toxicity has led to a recommendation to avoid remdesivir in patients with impaired renal function, but it is another risk/benefit situation to be determined for each patient.

IMPORTANT FACTS

- As with the anti-influenza antivirals, remdesivir seems to be most effective when started earlier in the course of infection, when viral replication is high. For patients whose disease has progressed to a need for mechanical ventilation, remdesivir is not beneficial. It may be beneficial earlier in the course of disease, but its IV-only administration limits its use for outpatients.
- A 5-day course of therapy for remdesivir appears to offer similar benefit to the originally studied 10-day course of therapy, although in some patients without improvement at day 5, treatment may be extended.
- Although remdesivir resistance can be selected for *in vitro* and has been documented in a handful of case reports, to date emergent resistance on therapy does not appear to be a significant concern with this agent.

What They’re Good For

Patients hospitalized with COVID-19 disease who do not require invasive mechanical ventilation.

Don’t Forget!

Although remdesivir may have a modest benefit in hospitalized patients with COVID-19, those agents with the greatest mortality benefit are those targeting the inflammatory response (dexamethasone, baricitinib, tocilizumab). Make those the priority for your most seriously ill patients.

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ANTIRETROVIRAL DRUGS

INTRODUCTION TO ANTIRETROVIRAL DRUGS

Despite the decades-long decrease in antibacterial drug development, one area that has seen substantial growth is the development of antiretroviral drugs targeting the HIV virus. Only a single active drug (zidovudine) was available near the beginning of the epidemic in the mid-1980s, and today more than two dozen drugs and drug combinations are available, with more in the pipeline. Most antiretroviral drug classes are in their second or greater generation of agents, leaving some of the earlier agents essentially obsolete. The development and proper usage of these agents have moved HIV infection—for those who can access antiretrovirals—into the realm of a chronic disease. More than any other antimicrobial group, however, the antiretrovirals come with the challenges of taking complex multidrug regimens for years: drug adherence, resistance, toxicities, and interactions. The full scope of these issues is beyond this text; instead, we will highlight key aspects of the drug classes and unique properties of individual agents, especially as related to toxicities. The treatment recommendations for HIV change at a dizzying pace; when determining whether a patient's regimen meets the most updated guidelines, we recommend you check the website at http://hivinfo.nih.gov. *Important note:* We present the commonly used abbreviations for these agents so that you may recognize them in practice, but it is not acceptable to use these abbreviations in prescriptions, and it is not recommended to use them in patient documentation.

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NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Agents: tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC), lamivudine (3TC), abacavir (ABC), *zidovudine (ZDV, AZT)*

Combinations (note: these are NRTI-only combinations—coformulations including other classes are discussed in those sections): emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada), abacavir/lamivudine (ABC/3TC, Epzicom), emtricitabine/tenofovir alafenamide (FTC/TAF, Descovy), lamivudine/zidovudine (3TC/ZDV, Combivir)

The nucleoside reverse transcriptase inhibitors (NRTIs) are the oldest class of antiretrovirals. (Tenofovir is technically a nucleotide but is grouped with these agents.) A combination of two of these drugs typically forms the “backbone” of most anti-HIV regimens.

Mechanism of Action

The NRTIs inhibit the action of the virally encoded protein reverse transcriptase by taking the place of nucleotides in the elongating strand of viral DNA, leading to early termination of the viral DNA strain.

Spectrum

In addition to being used to treat the HIV virus, several of these drugs (tenofovir, emtricitabine, lamivudine) have clinically useful activity against hepatitis B virus (HBV).

Adverse Effects

Hypersensitivity: In a minority of patients, abacavir use is associated with a hypersensitivity reaction manifesting with fever, rash, and flulike symptoms days to weeks after starting therapy. Continuation of or rechallenge with abacavir in patients experiencing this syndrome can be fatal. Presence of the HLA-B*:5701 allele is predictive of toxicity, and routine screening of patients for this genotype is now recommended before starting therapy; patients testing positive should not be offered abacavir and should have an allergy documented in their chart.

Renal: Nephrotoxicity, evidenced by increased serum creatinine and renal electrolyte and protein wasting, is a well-documented adverse effect of tenofovir and requires regular monitoring of renal function. The new formulation tenofovir alafenamide (TAF) appears to confer less toxicity risk than the tenofovir disoproxil fumarate (TDF) formulation.

Skeletal: Reduction in bone mineral density and risk of fracture is a concern with tenofovir, with greater risk among patients taking the TDF formulation.

Metabolic: While TAF is associated with less nephrotoxicity and skeletal effects than TDF, TAF is associated with more weight gain and an increase in cholesterol and triglycerides. Among older NRTIs, a constellation of toxicities thought to be related to effects on the mitochondria—including lactic acidosis, hepatic steatosis, and pancreatitis—were a significant concern. Agents with a higher propensity for this toxicity include zidovudine and the mostly obsolete agents didanosine and stavudine; the risk with current first-line NRTIs is low.

Hematologic: Bone marrow suppression (anemia, neutropenia) occurs frequently with zidovudine and rarely with other NRTIs.

IMPORTANT FACTS

- All the NRTIs with the exception of abacavir require dosage adjustment in renal dysfunction. This may require avoiding the fixed-dose combination preparations to give more dose flexibility. Note that thresholds for dose adjustment differ by specific agent.
- NRTIs have fewer metabolic drug interactions compared with the other antiretroviral drug classes. However, an important interaction to be aware of is a significant reduction in levels

of tenofovir when the TAF (but not the TDF) formulation is used with strong enzyme inducers (e.g., rifampin, phenytoin, carbamezapine).

- Various patterns of cross-resistance among the NRTIs occur. Expert interpretation of antiviral susceptibility is required, and in some cases NRTIs may confer a therapeutic benefit even for resistant viruses.
- The TAF formulation of tenofovir has a much lower dose than the TDF version. Careful attention to which formulation is planned to be used is important to avoid medication errors.
- Zidovudine is included here for its role in preventing mother-to-child transmission during delivery in patients who are not virologically suppressed at the time of delivery. Otherwise, this drug, which was the first anti-HIV antiretroviral and was formerly known as AZT, no longer has a place in routine HIV care.

What They're Good For

NRTIs are used as components of most combination antiretroviral regimens for HIV. For treatment-naïve patients, two NRTIs are typically combined with a drug from another class. For treatment-experienced patients, three or more NRTIs may be part of a salvage regimen. As noted, certain NRTIs are also used to manage HBV infections. Use of these drugs in management of HIV/HBV coinfected patients requires accounting for the overlap in activity between the viruses to ensure that resistance doesn't emerge because of suboptimal activity against one of the viruses.

Don't Forget!

The two-NRTI backbone has long been a staple of HIV regimens and is now easy to operationalize with coformulated pills, but alternative regimens are becoming more common. Some single-NRTI and no-NRTI regimens are now among the recommended regimens for treatment-naïve patients. However, regimens with less than two NRTIs should still warrant greater scrutiny to ensure they are not the result of an inadvertent medication error.

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NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Agents: etravirine (ETR), rilpivirine (RPV), doravirine (DOR), nevirapine (NVP), efavirenz (EFV)

Combinations: rilpivirine/tenofovir DF/emtricitabine (RPV/TDF/FTC, Complera), rilpivirine/dolutegravir (RPV/DTG, Juluca), rilpivirine/tenofovir AF/emtricitabine (RPV/TAF/FTC, Odefsey), rilpivirine/cabotegravir (RPV/CAB, Cabenuva [oral and IM]), doravirine/tenofovir DF/lamivudine (DOR/TDF/3TC, Delstrigo), efavirenz/tenofovir DF/emtricitabine (EFV/TDF/FTC, Atripla, Symfi)

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the same enzyme as the NRTIs but work through a different mechanism and have greatly different pharmacologic properties. That extra *N* makes a big difference—it's very important to keep the two drug classes straight.

Mechanism of Action

Instead of inhibiting the action of reverse transcriptase by "pretending" to be regular nucleosides, NNRTIs bind to a different part of the enzyme. The binding of the NNRTI causes a change in the conformation of the enzyme that interferes with its ability to form the viral DNA chain.

Spectrum

The only current clinical use is for HIV.

Adverse Effects

Dermatologic: Rashes can occur with all NNRTIs, although nevirapine appears to be the biggest offender. Though some mild forms can be treated with antihistamines, any lesions involving the mucous membranes (suggesting Stevens-Johnson syndrome or similar eruptions) must be managed urgently and represent an absolute contraindication to rechallenge.

Central nervous system (CNS): Efavirenz can cause a broad spectrum of CNS effects; common effects include dizziness, drowsiness (or sometimes insomnia), and abnormal (and especially vivid) dreams. Less common effects include depression, psychosis, and suicidal ideation. The onset of effects is usually very rapid (with the first few doses) and often subsides after several weeks of therapy. These effects may be minimized by taking the drug on an empty stomach and by taking at bedtime or 2–3 hours prior. A history of mental illness or depression is a relative contraindication to the use of efavirenz. CNS symptoms may occur but are less common with rilpivirine and doravirine.

Hepatotoxicity: All NNRTIs can cause a spectrum of hepatotoxicity, from asymptomatic transaminase elevations, to clinical hepatitis, to fulminant hepatic failure. Nevirapine-induced hepatotoxicity may occur in the context of a hypersensitivity reaction (see next). Monitoring of signs and symptoms of hepatitis and liver enzymes is important for all these agents.

Hypersensitivity: Nevirapine can cause a hypersensitivity reaction characterized by flulike symptoms, fever, jaundice, and abdominal pain, with or without a rash. Fulminant hepatic failure and severe rash (e.g., toxic epidermal necrolysis) are the most feared manifestations of nevirapine hypersensitivity reactions. Interestingly, this syndrome appears to be more frequent in patients who are less immunocompromised (have higher CD4 counts) when starting nevirapine. The risk of nevirapine hypersensitivity syndrome may be reduced by using a “reverse taper” upon drug initiation: Start with a lower dose and escalate to full dose over 2 weeks, when the risk is highest.

Injection site: The rilpivirine/cabotegravir combination has an intramuscular injection formulation (discussed more in the next section), and thus injection site reactions such as pain and swelling may occur but are typically self-limited.

Pregnancy/lactation: The FDA recommends women avoid efavirenz during pregnancy

because of potential fetal risk, although the CDC guidelines suggest patients whose infection is well controlled on efavirenz can continue the drug during pregnancy.

IMPORTANT FACTS

- A key limitation of NNRTIs has been the low “genetic barrier” to resistance. A single point mutation can lead to high-level resistance to the entire class of drugs. Thus, even stricter adherence may be necessary to NNRTI-based regimens to prevent the emergence of resistance. The advanced-generation agents etravirine and doravirine possess activity against viruses with some NNRTI mutations and may have roles for patients who have failed either other NNRTIs.
- NNRTIs have a much broader and more diverse drug interaction profile than the NRTIs. (Remember, one *N* makes a lot of difference!) Generally, nevirapine is an inducer of drug metabolism; efavirenz and etravirine show mixed inducing and inhibitory properties; and rilpivirine and doravirine are CYP P450 substrates but do not appear to have significant effects on metabolism of other drugs. Thus, careful screening of these drugs against all other agents in a patient’s regimen is warranted.
- Two NNRTI-containing combination agents offer NRTI-free treatment options in select patients. Rilpivirine plus the integrase inhibitor dolutegravir is an option for patients who have achieved full virologic suppression on a 3-drug regimen for at least 6 months. Rilpivirine plus the integrase inhibitor cabotegravir has two formulations: a once-daily tablet and a long-acting intramuscular coformulation designed to be administered as intermittent (once-monthly) maintenance therapy. Patients take 1 month of the oral formulation and then transition to once-monthly injections. In clinical trials to date, viral suppression has been similar to comparator daily pill regimens, and patients have preferred the once-monthly injections. If you have a patient in whom adherence is a concern, consider this treatment option.

What They’re Good For

Although NNRTI-based regimens have been displaced from the “initial recommendations for most patients” category by the integrase inhibitors, they have a number of useful applications. The rilpivirine/cabotegravir regimen offers an exciting new option for once-monthly therapy. For patients who experience adverse effects due to NRTIs, the ability to switch to a rilpivirine/dolutegravir regimen may be important. Doravirine and etravirine may be especially useful in treatment-experienced patients as part of a multidrug salvage regimen.

Don’t Forget!

NNRTI rashes can be no minor thing and can include the life-threatening Stevens-Johnson syndrome. Make sure to counsel patients starting on NNRTIs that they should report any rash to their healthcare provider, including blistering on mucous membranes such as the mouth and nose.

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PROTEASE INHIBITORS

Agents: darunavir (DRV), ritonavir (boosting dose: /r, full dose: RTV), atazanavir (ATV)

Combinations: darunavir/cobicistat (DRV/c, Prezcobix), darunavir/cobicistat/tenofovir AF/emtricitabine (DRV/c/TAF/FTC, Symtuza), atazanavir/cobicistat (ATV/c, Evotaz), lopinavir/ritonavir (LPV/r, Kaletra)

The introduction of the protease inhibitors (PIs) was a major advance in antiretroviral therapy. Combination regimens with PIs were the beginning of the era of "highly active antiretroviral therapy" (HAART) and have had a major impact on prolonging life span among HIV-infected individuals. (*Note:* The term *HAART* has fallen out of favor.) PIs are now entering their third generation, with more-potent agents having fewer acute toxicities; however, long-term toxicities are arising as a concern. A key advance has been the introduction of "boosting": using the (normally undesirable) potent inhibition of drug-metabolizing enzymes displayed by the antiretroviral ritonavir or the pharmacokinetic booster cobicistat to increase the serum concentrations and half-lives of other PIs. Boosting is routine for all PIs: Patients either take an additional pill of a low dose of ritonavir along with their PI (typically indicated as "/r," as in ATV/r) or a co-formulation with cobicistat ("/c," as in ATV/c) or ritonavir (as with LPV/r).

Mechanism of Action

When the hijacked HIV-infected cell uses the cell's ribosomes to synthesize its own proteins, some of them are created in long chains that need to be cut up into their component parts to

work correctly. Protease inhibitors selectively inhibit the viral enzyme (HIV protease) responsible for this processing. Think of protease enzymes as a pair of scissors that cut out prefabricated shapes from a piece of cardboard paper—destroy the scissors with a rock (that is, protease inhibitors) and the shapes are just a piece of paper.

Spectrum

Only current clinical use is for HIV. Protease inhibitors that treat hepatitis C virus (HCV) are different drugs and are not active against HIV, and vice versa.

Adverse Effects

Cardiovascular: Patients with HIV living long enough to suffer from heart attacks and strokes is viewed (somewhat perversely) as a sign of the success of potent antiretroviral therapy, particularly PIs. However, the possibility of cardiovascular adverse effects is now recognized as a substantial problem. PIs appear to interact with conventional cardiovascular risk factors to increase risk for myocardial infarction and stroke. Atazanavir and darunavir may confer somewhat lower risk compared with other PIs. Management—if switching to another class is not an option—is with all the mainstays of cardiovascular risk prevention (diet, exercise, drugs).

Gastrointestinal: All PIs are pretty hard on the GI tract (nausea, vomiting, diarrhea). Taking the drugs with food may reduce the symptoms somewhat. Many patients find the effects more tolerable with time. Severe cases may require administration with antiemetics or antidiarrheals.

Hepatotoxicity: The potential for hepatotoxicity exists with all PIs, ranging from asymptomatic transaminase elevations to clinical hepatitis.

Metabolic: One means by which PIs increase cardiovascular risk is through adverse effects on the lipid profile. The PIs may also be associated with lipodystrophy (fat accumulation in abdomen, breasts, and neck).

Nephrotoxicity: Renal toxicity caused by certain PIs precipitating in the kidneys or ureters has been reported. This toxicity risk may be higher with atazanavir. Adequate fluid intake is recommended for prevention. Of note, the pharmacokinetic enhancer cobicistat can increase serum creatinine through inhibition of tubular secretion, but the true glomerular filtration rate remains unchanged.

IMPORTANT FACTS

- Compared with the NNRTIs and integrase strand transfer inhibitors (INSTIs), PIs are more

robust to antiviral resistance. Typically, several mutations in the target enzyme are required to confer high-level resistance. Thus, PI-based regimens may be slightly more “forgiving” of less than perfect adherence—although, of course, that’s probably not the message to convey to your patients.

- The PIs pose tremendous drug interaction challenges. They are all substrates of the common drug-metabolizing enzymes and thus can have their concentrations substantially increased or decreased by drugs that inhibit or induce these enzymes. Generally, coadministering other drugs that are P450 substrates (such as statins, macrolides, benzodiazepines, and calcium channel blockers) with PI regimens boosted with ritonavir or cobicistat leads to increased serum concentrations of those drugs. However, more unpredictable effects can occur, perhaps as a result of shunting to alternative pathways or mixed inhibition/induction, leading to the reduction in serum levels of P450 substrates (as can be seen with the voriconazole–ritonavir interaction). The bottom line: For patients on PIs, carefully screen all of their medications for drug interactions using the most up-to-date references.
- Ritonavir is now used almost exclusively as a pharmacokinetic booster in much lower doses than its originally approved dose of 400 mg bid. It is not well tolerated at the higher dose, and the majority of prescriptions or orders for the 400-mg dose are an error. At the least, it warrants a double-check and a phone call.

What They’re Good For

Darunavir-based combinations are among the drugs recommended for initial therapy if integrase inhibitor-based regimens are not the best fit for the patient. An example could be if urgent initiation of therapy is required before genotyping for drug susceptibility can be performed or if transmitted integrase inhibitor resistance is suspected. Darunavir is generally preferred over atazanavir. PIs are frequently used in salvage regimens for patients with resistant virus. Their durable viral suppression needs to be balanced against their long-term toxicities and drug interaction profile.

Don’t Forget!

Unboosted protease inhibitors are a thing of the past. If there’s not a little ritonavir or cobicistat in the regimen, something is probably wrong.

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INTEGRASE INHIBITORS

Agents: dolutegravir (DTG), raltegravir (RAL), bictegravir (BIC), cabotegravir (CAB)

Combinations: dolutegravir/abacavir/lamivudine (DTG/ABC/3TC, Triumeq), dolutegravir/lamivudine (DTG/3TC, Dovato), rilpivirine/dolutegravir (RPV/DTG, Juluca), rilpivirine/cabotegravir (RPV/CAB, Cabenuva), bictegravir/tenofovir AF/emtricitabine (BIC/TAF/FTC, Biktarvy), elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/c/FTC/TDF, Stribild), elvitegravir/cobicistat/emtricitabine/tenofovir AF (EVG/c/FTC/TAF, Genvoya)

The integrase inhibitors (abbreviated as INSTI for integrase strand transfer inhibitors) went from a “new and promising” class of antiretrovirals (*Antibiotics Simplified, 3rd Edition*) to the anchor of all the CDC’s recommended regimens for initial therapy for most patients. They offer excellent tolerability, fewer drug interactions (except for elvitegravir), and one-pill, once-daily convenience (except for raltegravir). Their novel mechanism of action also provides a new option for treatment-experienced patients.

Mechanism of Action

After the HIV reverse transcriptase enzyme creates a strand of viral DNA, a viral protein called integrase facilitates the transfer of the HIV DNA into the host cell’s genome. The INSTIs inhibit this enzyme, preventing the viral DNA from becoming a part of the host cell enzyme, an

important step in HIV replication.

Spectrum

Only current clinical use is for HIV.

Adverse Effects

Musculoskeletal: Raltegravir and dolutegravir have been associated with increases in creatine phosphokinase. Most of these cases have been asymptomatic; clinically evident myositis or rhabdomyolysis is rare.

Central nervous system: Insomnia and depression have been reported with INSTI use.

Metabolic: Weight gain has been associated with the initiation of multiple classes of antiretrovirals, but appears to be particularly pronounced with INSTI use.

Renal: Cobicistat (formulated with elvitegravir) inhibits the renal secretion of creatinine, leading to increased levels of serum creatinine without a decline in glomerular filtration rate. It's important to differentiate this "fake" renal dysfunction from actual renal dysfunction, especially if the patient is also on tenofovir. Dolutegravir and bictegravir have also been associated with this phenomenon.

IMPORTANT FACTS

- Cobicistat isn't an antiviral but rather a "pharmacokinetic enhancer"; much like ritonavir, it is used to "boost" the concentrations of other drugs. Thus, concerns for drug interactions for the combination elvitegravir product are similar to those for ritonavir-boosted protease inhibitors. In contrast, raltegravir, dolutegravir, and bictegravir have few documented drug interactions—a considerable advantage over many antiretrovirals. An important exception to note is that strong enzyme-inducing agents like rifampin or phenytoin can lower all INSTI levels.
- A nonmetabolic drug interaction that the INSTIs share is reduced absorption when these drugs are coadministered with divalent and trivalent cations (the same kind of issue that affects fluoroquinolones and tetracyclines). Thus, careful attention to the timing of dosing must be paid in patients on INSTIs and antacids or multivitamin supplements. (The exact recommendations for spacing vary by INSTI and cation.)
- Among the INSTIs, bictegravir and dolutegravir have higher genetic barriers to resistance than raltegravir and elvitegravir.
- Note that elvitegravir is available as a combination product with "old tenofovir" (TDF) as

well as “new tenofovir” (TAF). Make sure you have the right one!

What They’re Good For

As noted, these drugs have rocketed to the top of the preferred list of antiretrovirals because of their many favorable characteristics. All four currently (2021) recommended “regimens for most people with HIV” are INSTI-based.

Don’t Forget!

Patients may be taking divalent/trivalent cations as antacids or vitamin supplements without those showing up on their medication profile. Make sure to ask patients if they are taking any of these agents before starting their INSTI regimen!

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ENTRY, ATTACHMENT, AND FUSION INHIBITORS

Agents: maraviroc (MVC), enfuvirtide (T-20 [SQ]), *ibalizumab (IBA)*, fostemsavir (FOS)

We will dip a toe into “antiretrovirals for experts only” by briefly discussing several structurally distinct agents that interfere with HIV’s attachment to and entry into the cell. These agents are generally reserved for treatment-experienced patients as part of complex salvage regimens.

Mechanism of Action

The process of HIV binding to and entering the cell involves a “handshake” between viral proteins and proteins on the host cell target. Fostemsavir binds to the gp120 glycoprotein on the surface of the HIV virion, preventing it from changing to the configuration necessary to bind to its target on human cells. Ibalizumab binds to and blocks the CD4 receptor on human cells that HIV binds to, while maraviroc similarly binds to one of the co-receptors (CCR5). After binding occurs, a multistep process leads to viral fusion with the cell; enfuviritide interferes with the process of fusion.

Spectrum

Only current clinical use is for HIV.

Adverse Effects

Dermatologic: Injection site reactions—including pain, erythema, pruritis, and nodule formation—occur in essentially all patients using subcutaneous enfuvirtide.

Hepatotoxicity: Maraviroc has a black box warning regarding hepatotoxicity, based on case reports from healthy subjects who received the drug in early clinical trials. The effect seems to be rare in patients treated with maraviroc. Transaminase and bilirubin elevations may be seen in patients on fostemsavir.

Cardiovascular: Fostemsavir may prolong the QTc interval; caution is warranted in patients with underlying heart disease or who are on concomitant QT-prolonging agents.

IMPORTANT FACTS

- Enfuvirtide is administered as a twice-daily subcutaneous injection associated with substantial injection site reactions; thus, it is generally reserved for patients with the most difficult-to-treat, multidrug-resistant strains of virus. Ibalizumab is administered as an every-two-weeks infusion and is currently used for treatment-experienced patients.
- Because maraviroc only blocks one of two coreceptors for HIV, it will not be effective for virus strains that primarily utilize the CXCR4 coreceptor for viral entry. Hence, before a patient is started on maraviroc, a tropism test must be performed to see whether the patient's virus "prefers" CCR5 (in which case maraviroc may be useful) or CXCR4 (thus ruling out maraviroc use).
- Maraviroc is a substrate of P450 drug-metabolizing enzymes and, thus, there are different dosage recommendations depending on which other potentially interacting drugs the patient is taking.

What They're Good For

These drugs are mainly for use in highly treatment-experienced patients.

Don't Forget!

Before initiating maraviroc, make sure you know its "Trofile"—that is, the name of the test used to determine the pro*file* of its *trop*ism (CCR5 vs CXCR4).

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ANTIVIRAL INTERFERONS

Agents: pegylated interferon-α 2a [SC], interferon- α 2a [SC], interferon-α 2b [SC]

Interferons are normal human cytokines that are used by the immune system to activate cells when infection is present, fight cancerous cells, and perform other functions. They are given exogenously in the treatment of multiple diseases, ranging from multiple sclerosis to cancers to viral hepatitis.

Mechanism of Action

Interferons have multiple mechanisms of action against hepatitis viruses. They have direct antiviral effects, change cellular differentiation, inhibit cell growth, activate macrophages, and increase lymphocyte cytotoxicity. Pegylated forms of interferon have had molecules of polyethylene glycol (PEG) attached to the interferon molecules to improve their pharmacokinetics by increasing their half-lives, allowing for decreased administration frequency.

Spectrum

Alpha interferons are used for the treatment of infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV).

Adverse Effects

Adverse effects are very common with interferons, leading to noncompliance, patient dropout, and avoidance of their use. Flulike symptoms are most common, including headache, fatigue, weakness, fever, and myalgia. Depression is also common and often requires pharmacologic treatment. Patients with suicidal ideation should not be given interferons. Anxiety can also occur. Hematologic adverse effects are also common with interferons, notably cytopenias including neutropenia, anemia, and thrombocytopenia. Interferons can worsen decompensated cirrhosis and are generally not administered to these patients.

IMPORTANT FACTS

- Pegylated interferons have supplanted nonpegylated forms for the treatment of viral hepatitis. Pegylated forms are given once weekly compared to thrice weekly for the nonpegylated interferons, improving compliance and convenience. Adverse effects are somewhat attenuated also, and efficacy is either similar or somewhat higher for the pegylated forms.
- Interferons commonly cause or exacerbate depression and are contraindicated in severe depression and patients contemplating suicide. There is generally no rush in the treatment of chronic HCV infection, so ensure that your patient's depression is controlled (pharmacologically if necessary) before starting therapy. For HBV infection, other drugs are better choices in depressed patients.

What They're Good For

Since the advent of new direct-acting antiviral agents for HCV, the use of interferons for this indication has declined substantially, and interferons are now rarely used. For chronic HBV infection, nucleoside/nucleotide analogs are preferred over pegylated interferons by many clinicians (and patients) due to their much better adverse effect profile, but they are taken indefinitely compared to a finite regimen for interferon.

Don't Forget!

Watch out for the many adverse effects of interferon therapy during treatment, and be vigilant in observing for emerging depression.

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DIRECT-ACTING ANTI-HEPATITIS C AGENTS

Agents: protease inhibitors: glecaprevir (GLE)*, grazoprevir (GZR)*, voxilaprevir (VOX)* NS5A inhibitors: velpatasvir (VEL)*, elbasvir (EBV)*, ledipasvir (LDV)*, pibrentasvir (PBR)*, NS5B (polymerase) inhibitors: sofosbuvir (SOF)*

***Agents available as part of fixed-dose combinations: grazoprevir/elbasvir (GBR/EBV, Zepatier), ledipasvir/sofosbuvir (LDV/SOF, Harvoni), glecaprevir/pibrentasvir (GLE/PBR, Mavyret), sofosbuvir/velpatasvir (SOF/VEL, Epclusa), sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX, Vosevi)**

The treatment of infections caused by chronic hepatitis C virus (HCV) has undergone as big of a revolution in therapy as HIV treatment has—but instead of unfolding over four decades, it has unfolded over one.

Two serine protease inhibitors introduced in late 2011 (boceprevir, telaprevir) heralded this new era—and are now obsolete as we are now on the third generation of agents, with the newest agents being more potent, better tolerated, and more convenient. As with HIV treatment, treatment regimens using these drugs typically consist of multiple agents with different mechanisms of action. In contrast to HIV regimens, the treatment duration for these

anti-HCV treatments is on the order of only 3–4 months in most patients, with cure rates ranging from 80 to 100%. Compared to prior ribavirin plus interferon-based regimens for HCV, the new drugs are *much* better tolerated, but they still have important cautions for drug interactions and possible adverse effects.

Mechanism of Action

Along with ribavirin, these agents are considered to be direct-acting antivirals (DAAs)—to distinguish them from the indirect anti-HCV effects of interferon. Their mechanisms are varied: Some inhibit proteases; others inhibit RNA polymerases (NS5B protein—"NS" stands for "non-structural"); and in the case of the NS5A inhibitors, it's not exactly clear how they work. Following the model of the latest HIV therapies, most of the agents are coformulated in fixed combinations, which reduces the need to select drugs with different mechanisms "from the menu."

Spectrum

There are at least 6 HCV genotypes that can cause infection in humans, and the DAAs differ in their activity against each. Genotype 1 (which comes in 1a and 1b flavors) is the most prevalent in the United States, and as such each of the current regimens has activity against these. Other genotypes are less common, but some regimens are not active against every genotype. The *pan-genotypic* regimens that provide activity against all genotypes in treatment-naïve patients are glecaprevir/pibrentasvir and sofosbuvir/velpatasvir (with or without voxilaprevir). If other regimens are used for treatment, genotyping is required to ensure the patient is infected with a genotype that is susceptible to that regimen.

Adverse Effects

Besides their potent activity, the substantially greater tolerability of these drugs relative to ribavirin and interferon is responsible for their having rapidly become the regimens of choice. Most agents are well tolerated and typically associated with mild toxicities, including nausea, vomiting, and fatigue.

> ***Hepatotoxicity***: Protease-inhibitor containing regimens (elbasvir/grazoprevir and glecaprevir/pibrentasvir) have been associated with hepatic decompensation in some patients. Close monitoring of ALT is indicated, with treatment interruption recommended for substantial asymptomatic elevations (e.g., >10-fold of upper limit of normal) or lower elevations that are associated with symptoms of hepatitis (e.g., jaundice, nausea, vomiting, abdominal pain). Protease inhibitor–containing regimens are not recommended for patients with decompensated cirrhosis. Initiation of HCV therapy has also been associated with reactivation of quiescent hepatitis B infection in patients receiving any DAA regimen. Patients who are baseline HBV positive require careful monitoring.

IMPORTANT FACTS

- Having a hard time keeping straight the protease inhibitors, NS5A inhibitors, and NS5B inhibitors? Protease inhibitors have a "-*pr*evir" suffix (*pr* for *pr*otease), NS5*A* inhibitors have a "-*a*svir" suffix, and NS5*B* inhibitors have a "-*b*uvir" suffix. Don't you wish all drugs were that easy?
- As with HIV antiretrovirals, drug interactions are a concern, falling into two main categories. The protease inhibitors, similarly to the HIV protease inhibitors, are substrates and inhibitors of CYP 3A4 with whole constellation of drug interactions that entails. The NS5A and B inhibitors are less problematic in that domain but are sensitive to coadministration with acid-reducing agents. Luckily the website www.hep-druginteractions.org can help you navigate all manner of potential interactions, including the especially tricky HIV–HCV cotreatment challenges.
- Resistance to these agents rarely emerges during therapy but does seem to correlate with failure to eradicate HCV. Resistance seems to be a greater concern with the NS5A inhibitors, and baseline resistance-associated substitution (RAS) testing is recommend before initiation of NS5A inhibitors, depending on the drug and patient history (e.g., treatment-experienced). Use of sofosbuvir/velpatasvir/voxiloprevir, addition of ribavirin, and extension of duration of treatment are potential options for patients with drug resistance. In many cases, resistance may have emerged during treatment with less-potent, prior-generation DAAs.

What They're Good For

These drugs are used in the treatment of patients with chronic HCV infection, where they are typically associated with a high rate of cure. Specifics of treatment selection are complex; recommendations are regularly updated at www.hcvguidelines.org.

Don't Forget!

These drugs represent a true breakthrough in treating HCV, but the drugs are expensive (meaning they may get only one shot at therapy) and drug interactions are problematic, so patients need all the help they can get to make sure they get the most out of their treatment course.

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RIBAVIRIN

Agent: ribavirin

Ribavirin is an antiviral agent that is active against many different types of viruses, though it is used primarily for the treatment of hepatitis C virus (HCV) and respiratory syncytial virus (RSV) infection. The addition of ribavirin to some other agents for HCV treatment increases both the effectiveness and toxicity of treatment.

Mechanism of Action

The mechanism of action of ribavirin is not well characterized, but it is a nucleoside analogue of guanosine that is phosphorylated into its active form inside cells. Technically it is a direct-acting anti-HCV antiviral like those discussed in Chapter 41 but is generally considered separately from those agents.

Spectrum

Well-characterized activity has been described for HCV and RSV, though ribavirin has some activity against other viruses and usually is the first in line for testing when some new virus emerges. (It was tried for SARS-CoV-2 and it didn't work.)

Adverse Effects

The main adverse effect of ribavirin is hemolytic anemia. This effect is dose related, dose limiting, and may be severe. Ribavirin is also associated with fatigue, headaches, and insomnia, though much of this data comes from studies of combination therapy with interferon, making attribution of causality difficult.

IMPORTANT FACTS

- For the treatment of HCV infection, ribavirin must always be used in combination. As monotherapy, ribavirin rapidly leads to resistant mutants of HCV.
- Ribavirin is usually administered orally, but it can also be given in an aerosolized form to patients with pulmonary RSV infection, principally in young children and in immunocompromised adults, most notably patients with lung or hematopoietic stem cell transplants. Administration via this route is technically complex, since efforts need to be made to reduce the environmental exposure of ribavirin—a known teratogen. Recent studies suggest that orally administered ribavirin may be similarly effective for treatment of RSV, and many centers are moving away from inhaled administration, at least in adults.
- Ribavirin causes birth defects and is contraindicated in pregnancy. Women of childbearing age taking ribavirin should use reliable contraception. Pregnant women must also avoid aerosolized ribavirin, and pregnant healthcare workers should avoid caring for patients receiving it, if possible.
- The primary means of managing ribavirin-induced anemia is dose reduction. If anemia becomes severe or persistent, erythropoietin can be given.

What It’s Good For

Ribavirin is used as part of combination therapies for some patients with HCV chronic infection. Ribavirin (aerosolized or oral) is used to treat severe RSV in both children and adults, primarily immunocompromised patients or those with severe comorbidities.

Don’t Forget!

Hemoglobin concentrations must be closely watched during ribavirin therapy. Expect some degree of anemia to occur and be prepared to act accordingly.

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HEPATITIS B NUCLEOSIDE ANALOGS

Agents: entecavir, tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF], lamivudine, adefovir

Analogs of viral nucleosides are useful not just for the treatment of HIV infection but for HBV infection as well. Because HBV is a DNA virus, these drugs can compete for viral enzymes with native viral nucleosides just as they do for reverse transcriptase in HIV. Several of them are active in both HIV and HBV infection, which is both a potential bonus and a potential pitfall for patients who are infected with both viruses. All are easy-to-take drugs that have changed the management of HBV to offer a regimen that is unlikely to eradicate HBV but well tolerated for long-term therapy and reduces disease progression. Tenofovir and lamivudine are extensively discussed in Chapter 39, so we will focus on entecavir and adefovir here.

Mechanism of Action

Nucleoside analogs inhibit the action of viral DNA polymerase by taking the place of nucleotides in the elongating strand of viral DNA, leading to early termination of the viral DNA strain.

Spectrum

Entecavir and adefovir are active against HBV and weakly active against HIV. They should not be used to treat patients coinfected with HBV and HIV because of the risk of selecting for resistant virus (unless they are on a separate fully suppressive HIV regimen).

Adverse Effects

These agents are generally well tolerated by most patients and have a low incidence of adverse effects. Adefovir can cause nephrotoxicity. The syndrome of lactic acidosis and hepatic steatosis is rare. Development of resistance to these agents can lead to an HBV reactivation "flare," with increases in transaminases and a rebound of viral load. Tenofovir and lamivudine toxicities are covered in Chapter 39.

IMPORTANT FACTS

- Patients planned to be initiated on any of these drugs for either HIV or HBV need to be tested for both before starting therapy.
- For tenofovir, both the TDF and TAF formulations can be used for HBV.

What They're Good For

Entecavir is a first-line therapy for patients with HBV (without HIV coinfection). Tenofovir is preferred for HIV coinfected patients. Lamivudine was previously a recommended agent, but there is a high risk of emergence of resistance, so it is no longer a preferred option. Adefovir is obsolete and no longer recommended.

Don't Forget!

Prevention is better than treatment! Be an advocate for hepatitis B vaccination for your unvaccinated, at-risk patients!

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ANTI-SARS-COV-2 ANTIBODY THERAPIES

Agents: *sotrovimab, tixagevimab/cilgavimab, bamlanivimab/etesvimab, casirivimab/imdevimab*

Normally we don't include drugs that aren't fully FDA-approved (at the time of writing) in *Antibiotics Simplified*. However, the use of monoclonal antibody (mAb) therapy for COVID-19 infection is not only a key tool in control of the disease but also a potential preview of the future role of mAbs as therapy for a variety of infectious diseases. It will be very important, though, to check your local epidemiology at the time as several agents in this class have already become obsolete as resistant variants emerge.

Mechanism of Action

These antibodies bind to specific epitopes on the receptor-binding domains (RBDs) of the SARS-CoV-2 spike protein, interfering with the interaction between the spike protein and the ACE-2 receptor on human cells. The different products bind to slightly different epitopes and thus may have varying activity against different variants of SARS-CoV-2.

Spectrum

Activity of mAbs can change substantially as new variants emerge; readers should double-check that the agents of interest are active against the predominant variant in the region.

Sotrovimab: SARS-CoV-2 (all variants up to and including Omicron), SARS-CoV-1

Bamlanivimab/etesvimab and casirivimab/imdevimab: SARS-CoV-2 (variants not including Omicron)

Tixagevimab/cilgavimab: SARS-CoV-2 (most variants but with marginal activity versus Omicron)

Adverse Effects

Hypersensitivity reactions: Infusion-related reactions, including rare instances of anaphylaxis, have occurred during mAb therapy. Current recommendations are that patients should be monitored in a healthcare setting for at least an hour after drug administration.

IMPORTANT FACTS

- At the time of writing, these drugs are being used in the United States under Emergency Use Authorization (EUA), a sort of astral plane between purely investigational drugs and fully FDA-approved therapies. There are others being considered for EUAs, and it is likely that these agents will continue to be produced and retired as SARS-CoV-2 variants evolve.
- Sotrovirmab, bamlanivimab/etesvimab, and casirivimab/imdevimab are given as intravenous infusions; in addition, casirivimab/imdevimab can be administered as a subcutaneous injection. However, fewer data supports subcutaneous use, and while it doesn't require placement of an intravenous line, it's still not fun: four 2.5 mL subcutaneous injections at different sites.
- Tixagevimab/cilgavimab is an intramuscularly administered, long-acting mAb designed for use as pre-exposure prophylaxis in patients who can't receive COVID-19 vaccines or who may not mount an adequate immune response to COVID-19 vaccination (for example, organ transplant recipients).

What They're Good For

As of press time, sotrovirmab, bamlanivimab/etesvimab, and casirivimab/imdevimab were all granted EUAs for prevention of hospitalization and death in SARS-CoV-2-infected patients at high risk for severe progression to severe disease—although only sotrovirmab is active against the Omicron variant currently becoming dominant. Casirivimab/imdevimab also has an EUA for post-exposure prophylaxis among patients who are unvaccinated against COVID-19 (or who have immunocompromising conditions) and who have a recent exposure to a SARS-CoV-2–infected patient. Tixagevimab/cilgavimab is authorized for pre-exposure prophylaxis in high-risk

patients not likely to be protected by vaccination.

Don’t Forget!

Trials to date suggest these mAbs are most effective *early*—either as prophylaxis or early therapy in high-risk patients. Help eligible patients get connected to care as soon as possible after their diagnosis.

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PART 6

ANTIPARASITIC DRUGS

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45 ANTIPARASITIC DRUGS

INTRODUCTION TO ANTIPARASITIC DRUGS

There is a tremendously unequal variation in the human burden of parasitic disease, based on geography, industrialization/hygiene, and immune status. It is estimated that up to half of the world's population is chronically infected with parasites. The extent of parasite-related morbidity and mortality depends on parasite burden, preexisting immunity, and patient comorbidities. We focus on parasitic diseases primarily affecting inhabitants of industrialized nations. Parasites causing human disease can be broadly grouped into two main categories: the unicellular protozoa and the multicellular helminths (**TABLE 45-1**). The protozoa have many subgroups, but we present them as primarily intestinal or primarily extraintestinal pathogens. The helminths are subdivided into nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms). Examples of common pathogens for each group are given along with some of the agents used in their treatment. Although not technically considered parasites, two other organisms that are susceptible to antiparasitic drugs also are addressed: *Pneumocystis jirovecii* (technically a fungus) and *Sarcoptes scabiei* (the scabies mite, technically an arachnid).

TABLE 45-1 | **Grouping of Parasites with Commonly Encountered Pathogens and Commonly Used Antiparasitic Agents**

Group	Subgroup	Examples	Antiparasitics*
Protozoa	Extraintestinal	*Plasmodium* (malaria) *Toxoplasma*	**Quinolines** Doxycycline Clindamycin **Atovaquone-proguanil** **Artemisins** Pyrimethamine/Sulfadiazine TMP/SMX
		Trypansoma	**Pentamidine**
	Intestinal	*Entamoeba* *Giardia* *Cryptosporidium*	Metronidazole Tinidazole *Paromomycin*
Helminths	Nematodes	*Ascaris* *Strongyloides*	**Albendazole** **Ivermectin**
	Trematodes	*Schistosoma*	*Praziquantel*
	Cestodes	*Echinococcus* *Taenia*	**Albendazole** *Praziquantel*
Other organisms	Fungus	*Pneumocystis*	TMP/SMX Clindamycin/**Primaquine** **Atovaquone** **Pentamidine**
	Ectoparasites	Scabies	**Ivermectin**

* Agents in **bold** are discussed in Part 6; agents in normal type are covered in other chapters; agents in *italics* are not discussed in this book.

Description

Drugs with antiparasitic activity range from everyday antibacterial drugs (metronidazole, doxycycline) to mildly exciting agents seen occasionally in routine practice (chloroquine, pentamidine) to the most exotic agents that can be obtained only from the Centers for Disease Control and Prevention (CDC) in the United States (diethylcarbamazine, sodium stibogluconate). In Part 6 of this book we will focus on the middle category, leaving the details of antibacterial drugs to their own chapters and the exotic agents to those with a keen interest.

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46 QUINOLINES

Agents: chloroquine, mefloquine, quinine, primaquine

The quinoline agents are among the oldest antiinfective agents used by humans, with recorded use of the bark of the *Cinchona* tree (imported from Peru) to treat fever in malarious areas of Europe dating back to the seventeenth century. The primary component of this remedy was quinine, the first antimalarial agent to be widely used. Although malaria is no longer endemic to most industrialized countries, it is considered to be the most important cause of fever in returning travelers, especially those not native to endemic areas, because of the potential for severe illness. There are important differences between the quinolines in activity based on both the species of *Plasmodium* and the geographic area; readers are advised to consult their updated national guidelines when managing suspected malaria cases.

Mechanism of Action

The mechanisms of action of quinolines on parasites are incompletely understood. Chloroquine and quinine appear to interfere with the ability of the malaria parasite to detoxify hemoglobin metabolites. Primaquine appears to affect parasitic mitochondrial function.

Spectrum

Protozoa (activity variable by region): Plasmodium falciparum, Plasmodium malariae,

Plasmodium ovale, Plasmodium vivax

Like-a-parasite-but-technically-a-fungus: Pneumocystis jirovecii (primaquine)

Adverse Effects

Cardiovascular: The quinolines can cause dose-related cardiovascular toxicity, including QT interval prolongation, hypotension, and potentially fatal ventricular arrhythmias.

Hematologic: Primaquine can cause hemolysis in patients deficient in glucose-6-phosphate dehydrogenase (G6PD); testing for G6PD deficiency is required before use.

Metabolic: Quinine can cause profound hypoglycemia resulting from the stimulated release of insulin.

Psychiatric: Mefloquine is associated with a range of psychiatric disturbances ranging from insomnia, vivid dreams, and mood swings to depression, psychosis, and suicide. Although mefloquine is well tolerated by the vast majority of patients taking the drug, patients with a history of psychiatric issues, including depression, should avoid taking mefloquine.

Systemic: The syndrome of “cinchonism” (tinnitus, headache, nausea, and visual disturbances) is common in patients receiving therapeutic doses of quinine. These effects can lead to discontinuation of therapy because of intolerance, but they resolve after drug discontinuation.

IMPORTANT FACTS

- In the United States, the manufacture of intravenous quinidine, previously recommended for initial treatment of severe malaria, has been discontinued. Intravenous artesunate (see Chapter 51) is now recommended as standard therapy for severe malaria where available.
- Unlike other antimalarial drugs, primaquine is active against the “hypnozoite” forms of *P vivax* and *P ovale*, which can lay dormant in the liver and cause relapsing infections. Thus, a 2-week course of primaquine is added to the antimalarial regimen when infection with these species is documented.

What They’re Good For

Chloroquine/hydroxychloroquine: Treatment of uncomplicated malaria (chloroquine, hydroxychloroquine) acquired in chloroquine-sensitive areas (only a few regions) and prophylaxis (chloroquine) against malaria in travelers to those regions.

Mefloquine: Treatment of uncomplicated malaria acquired in mefloquine-sensitive areas

(most of the world except Southeast Asia) and prophylaxis against malaria in travelers to those regions; mefloquine is generally a last-line treatment option due to its increased risk of adverse effects.

Quinine: Treatment of uncomplicated malaria in combination with doxycycline, tetracycline, or clindamycin; not used for prophylaxis.

Primaquine: Treatment of uncomplicated malaria due to *P vivax* or *P ovale* in combination with another agent; prophylaxis against malaria in travelers where *P vivax* is the principal species; and in treatment of mild-to-moderate *Pneumocystis* pneumonia in combination with clindamycin.

Don’t Forget!

As with bacterial infections, the progression of antimicrobial resistance makes treatment of and prophylaxis against malaria difficult. Because most clinicians deal with malaria infrequently, there is no shame in double-checking national guidelines to make sure you are using the most appropriate regimen for your patient. The CDC even has a malaria hotline to help clinicians deal with treatment of cases [business hours (855) 856-4713; after hours (770) 488-7788].

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ATOVAQUONE

Agents: atovaquone, atovaquone/proguanil

Atovaquone is an antiparasitic agent with activity against several important protozoans. Its activity against the malaria parasite is enhanced when given in combination with the drug proguanil. (This coformulated tablet is known as Malarone.) Atovaquone tends to be better tolerated than comparator drugs but is limited by the lack of an IV formulation (for severe disease), high cost, and somewhat lower efficacy (for *Pneumocystis* disease).

Mechanism of Action

Atovaquone appears to interfere with electron transport in the parasitic mitochondria.

Spectrum

Like-a-parasite-but-technically-a-fungus: Pneumocystis jirovecii

Protozoa: Plasmodium species, *Toxoplasma gondii, Babesia* species

Adverse Effects

Both atovaquone and atovaquone/proguanil are very well tolerated. The most common adverse

effects are gastrointestinal (nausea/vomiting, diarrhea, abdominal pain).

IMPORTANT FACTS

- Atovaquone is available as a suspension, whereas atovaquone/proguanil is formulated as a tablet. Bioavailability is rather low with both, but it is enhanced substantially when given with food, especially high-fat meals. Both agents should be administered with food.
- In clinical trials of atovaquone in treating mild-to-moderate *Pneumocystis* pneumonia in patients intolerant of TMP/SMX, atovaquone was slightly less effective than its comparators (dapsone or pentamidine) but better tolerated, leading to similar overall success rates. Atovaquone should not be used in patients with severe *Pneumocystis* pneumonia or in patients whose GI absorption is thought to be poor.
- Other than its cost, atovaquone/proguanil is a favorable drug for malaria prophylaxis for travelers. It is highly effective, well tolerated, active against chloroquine-resistant *Plasmodium*, and requires administration only 1–2 days prior to travel, while in the malaria-endemic area, and for 7 days after return. Many other agents used for malaria prophylaxis require beginning the medication 2 weeks before travel and continuing for 4 weeks afterward.

What They’re Good For

Atovaquone: Treatment of mild-to-moderate *Pneumocystis* pneumonia; prophylaxis against *Pneumocystis* in patients intolerant of first-line therapy; treatment of babesiosis in combination with azithromycin

Atovaquone/proguanil: Treatment of uncomplicated malaria and prophylaxis against malaria

Don’t Forget!

Make sure your patients take their atovaquone with food (or at the very least a glass of milk); the bioavailability of atovaquone is increased approximately five times when administered with food compared with the fasting state.

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BENZIMIDAZOLES

Agents: albendazole, mebendazole

Benzimidazoles are used primarily to treat infections caused by helminths (worms), ranging from the common pinworms found in children to pathogens causing massive cystic lesions in the brain. Most intestinal worm infections can be cured with a single dose of these drugs; for tissue-invasive disease, prolonged courses are necessary.

Mechanism of Action

The benzimidazoles interfere with elongation of the microtubules that are responsible for parasitic cellular structure, leading to a disruption of growth and division.

Spectrum

Nematodes (roundworms): Ascaris lumbricoides (roundworm), *Enterobius vermicularis* (pinworm), *Necator americanus* (hookworm), *Strongyloides stercoralis* (threadworm)

Cestodes (tapeworms): Echinococcus (liver abscess), *Taenia solium* (neurocysticercosis)

Adverse Effects

Albendazole is very well tolerated, especially when used as single-dose therapy in treatment of intestinal worm infection. With multidose regimens, adverse effects are primarily gastrointestinal, although hepatotoxicity and neutropenia are rarely reported. These drugs should generally be avoided in pregnancy, although some data suggest that they may be safe after the first trimester.

IMPORTANT FACTS

- Although data are limited, these drugs appear to be substrates of the cytochrome P450 system. Thus, it is possible that coadministration with strong inducers of drug-metabolizing enzymes such as phenytoin and rifampin may lower serum levels. Oral absorption of albendazole is limited, which generally does not pose a problem for treatment of intestinal nematode infections, and thus drug interactions would not be of concern. However, in treatment of systemic infections, caution is advised with coadministration of enzyme-inducing agents because of the potential for subtherapeutic drug levels.

What They’re Good For

As a single-dose therapy of most intestinal nematode infections, as an alternative for treatment of *Strongyloides* infection, and as treatment for tissue-invasive *Echinococcus* or *Taenia* infection.

Don’t Forget!

For some parasitic infections, drug-induced killing of the parasite releases antigens that can cause allergic reactions. Corticosteroids are sometimes administered to mitigate this effect. Know which infections this applies to before using antiparasitics for invasive infections.

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PENTAMIDINE

Agent: *pentamidine*

Pentamidine is the primary alternative to trimethoprim/sulfamethoxazole (TMP/SMX) for patients with *Pneumocystis* pneumonia, which was once an extremely common cause of severe pneumonia in HIV-infected patients. *Pneumocystis* pneumonia is becoming less common in HIV-infected patients due to the increased effectiveness of antiretroviral therapy, but of greater concern now in the solid organ and cancer chemotherapy populations as those patient groups expand. Pentamidine can be very toxic, so familiarity with its extensive adverse effects is required. It can be given either intravenously or by inhalation, and the proper route depends upon the indication.

Mechanism of Action

Pentamidine appears to bind to and disrupt the function of transfer RNA, resulting in inhibition of protein synthesis.

Spectrum

Like-a-parasite-but-technically-a-fungus: Pneumocystis jirovecii

Protozoa: Trypanosoma, Leishmania

Adverse Effects (IV pentamidine)

Cardiovascular: Hypotension can occur with rapid infusion of pentamidine; the drug should be infused over at least an hour. Cases of QT prolongation with ventricular arrhythmia have also been reported.

Metabolic: Pentamidine is toxic to the pancreas, leading to dysglycemias in up to 25% of patients. The course of this toxicity may initially manifest as hypoglycemia because pentamidine-induced pancreatic injury causes release of insulin from islet cells. Later, continuing injury can cause a decrease in pancreatic function, with hypoinsulinemia and hyperglycemia. Continued use may lead to irreversible damage, leaving patients with diabetes mellitus. Other manifestations of pancreatitis may also occur.

Renal: Nephrotoxicity is common with pentamidine, although it is generally reversible upon drug discontinuation. Electrolyte disturbances, including hypokalemia and hypocalcemia, may also occur.

Respiratory: Administration of pentamidine as an inhalation may induce bronchoconstriction, especially in patients with asthma. Pretreatment with an inhaled bronchodilator may attenuate these effects.

IMPORTANT FACTS

- In clinical trials of pentamidine as treatment for *Pneumocystis* pneumonia, pentamidine appeared to be about equal in efficacy to TMP/SMX; however, only about half of patients could tolerate a full course of IV pentamidine without discontinuing the drug or decreasing the dose. Careful monitoring (ECG, metabolic panel) and supportive care interventions (electrolyte replacement, glucose, or insulin as appropriate) are necessary. Also, dosage adjustment in patients with renal insufficiency is recommended.
- Once-monthly inhaled pentamidine has reasonable efficacy as a second-line agent for prophylaxis against *Pneumocystis* pneumonia. However, unlike with TMP/SMX prophylaxis, cases of extrapulmonary *Pneumocystis* infection have been reported in patients on inhaled pentamidine. Inhaled pentamidine also does not protect against *Toxoplasma* disease or bacterial pneumonia as TMP/SMX does.

What It’s Good For

IV pentamidine is an alternative drug for treatment of severe *Pneumocystis* pneumonia; inhaled pentamidine is an alternative for prophylaxis against *Pneumocystis* pneumonia. IV pentamidine is an alternative drug for treatment of leishmaniasis and trypanosomiasis.

Don’t Forget!

Watch out for overlapping toxicities with pentamidine and other drugs the patient may be on. Patients receiving pentamidine are often severely ill and may be on drugs like insulin, furosemide, aminoglycosides, and antiarrhythmics that may exacerbate pentamidine’s myriad adverse effects.

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IVERMECTIN

Agent: ivermectin

If you practice in a healthcare institution, you will likely be treated to at least one scabies outbreak over your career, if not one each year. While scabies is most often treated with permethrin cream, patients or their healthcare providers who are unable or unwilling to baste themselves in the cream will receive oral ivermectin. Ivermectin is also given to patients with the highly contagious crusted or “Norwegian scabies” (an unwarranted aspersion on Scandinavian hygiene). In addition to scabies, ivermectin is also effective in treating several diseases that may be endemic in tropical settings, such as the causative agents of river blindness, strongyloidiasis, and cutaneous larva migrans, the latter two of which occur, if infrequently, in the United States. It can also be used for treatment of *Strongyloides* hyperinfection syndrome, an increasingly recognized cause of life-threatening illness in immunocompromised patients.

Mechanism of Action

Ivermectin binds to the parasitic neuromuscular junction, causing muscular paralysis of the parasite. The parasite dies directly from the effects or from starvation.

Spectrum

Ectoparasites: Sarcoptes scabiei (scabies mite), *Pediculus humanus* (lice)

Nematodes (roundworms): Onchocerca volvulus (river blindness), *Strongyloides stercoralis* (strongyloidiasis), *Ancylostomiasis braziliense* (cutaneous larva migrans), other nematodes

Adverse Effects

In treatment of scabies, ivermectin is very well tolerated. Severe adverse reactions, including fever, myalgia, and hypotension, have been reported when ivermectin is used for management of nematode infections in endemic settings. These effects are thought to be a result of the host's immune response to antigens released from killed parasites. These effects are more severe in patients with higher worm burdens, and they generally resolve soon after drug administration.

IMPORTANT FACTS

- Yes, ivermectin is the same drug you use to treat your dog's heartworms. It is also at the center of a heart*worming* story: After ivermectin was shown to be effective as a once-yearly treatment for river blindness, the pharmaceutical company Merck offered to donate —free of charge—as much ivermectin as was needed to treat the disease. It is estimated that 200-million free treatments have been provided to date, avoiding more than half a million cases of blindness. Hey, at this point in the book, we figured you could use some good news (and bad puns).

What It's Good For

Ivermectin is used as an alternative to topical permethrin for scabies infection, as an alternative to topical therapies for treatment of head or body louse infestation, and for treatment of *Ancylostoma* infections. It is also a drug of choice for infection caused by *Strongyloides* or *Onchocerca*.

Don't Forget!

For treatment of ectoparasitic (scabies or lice) infestation, ivermectin should be administered as two doses, approximately 1 week apart. Administration of a single dose increases the risk of relapse.

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51 ARTEMISININS

Agent: *artesunate*, artemether/lumefantrine

As with the quinolines, the initial uses of artemisinins for treatment of malaria date back hundreds if not thousands of years—in this case in the form of the Chinese herb qinghao (*Artemisia annua*). In the 1970s, faced with increasing chloroquine resistance, Chinese scientists turned to the study of qinghao and were able to isolate the active agent, artemisinin. Further work led to the forms primarily used today, artesunate and artemether, which are now first-line antimalarials in much of the world, typically as artemisinin combination therapy (ACT) coformulations such as artemether/lumefantrine.

Mechanism of Action

The exact mechanism of antiparasitic effect of the artemisinins is not known, but it seems to involve production of reactive oxygen species after activation by heme inside erythrocytes. Artemisinins have rapid parasiticidal activity on multiple intraerythrocytic stages of the malaria parasite.

Spectrum

Protozoans: Plasmodium spp (malaria)

Adverse Effects

Intravenous artesunate is very well tolerated. Delayed hemolytic anemia has occasionally been observed, and patients should have weekly complete blood counts for 4 weeks after IV artesunate to monitor for this adverse effect.

IMPORTANT FACTS

- Although artesunate acts rapidly to bring down malarial load and improve symptoms of severe malaria, it has a short half-life, and using only the standard three-dose regimen can be associated with relapse. IV artesunate treatment should be followed by use of an appropriate oral antimalarial regimen (e.g., artemether/lumefantrine, atovaquone/proguanil). For non-severe malaria, a 3-day regimen of artemether/lumefantrine is sufficient, since the longer-acting lumefantrine provides prolonged residual activity against surviving parasites.
- Artemisinins are highly active against chloroquine- and mefloquine-resistant strains of malaria; unfortunately, artemisinin resistance has begun emerging in some areas of the world. Typically patients will continue to display a good initial response to therapy but have a higher parasite burden to which the partner drug is exposed, increasing the potential for emergent resistance and recrudescence of symptoms.
- Artemisinins have been studied for a variety of non-malarial indications, ranging from cytomegalovirus infections, to amoebic infections (e.g., the “brain-eating parasite” *Naegleria fowleri*), to cancer, to, of course, COVID-19. Whether hints of efficacy in any of these disease states eventually translates into broad clinical utility will be interesting to watch.
- For many years intravenous artesunate has been available only in the United States from the Centers for Disease Control and Prevention (CDC), but now it can be obtained from the manufacturer. However, many hospitals may not stock this uncommonly used agent, so urgent late-night phone calls and expedited shipping are still a frequent part of the severe malaria treatment experience (see https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html).

What It’s Good For

Intravenous artesunate is used in the United States for treatment of severe malaria—in other countries oral or rectal forms may be available. Artemether/lumefantrine is used for treatment of known or suspected chloroquine-resistant malaria; it is also recommended for initial treatment of severe malaria if IV artesunate is not immediately available. Artemisinins are not used for malaria chemoprophylaxis.

Don’t Forget!

If you are involved in treating a patient with severe malaria with intravenous artesunate, don’t get so caught up in the excitement that you forget to follow up with treatment with an oral agent; otherwise, the patient may experience a relapse.

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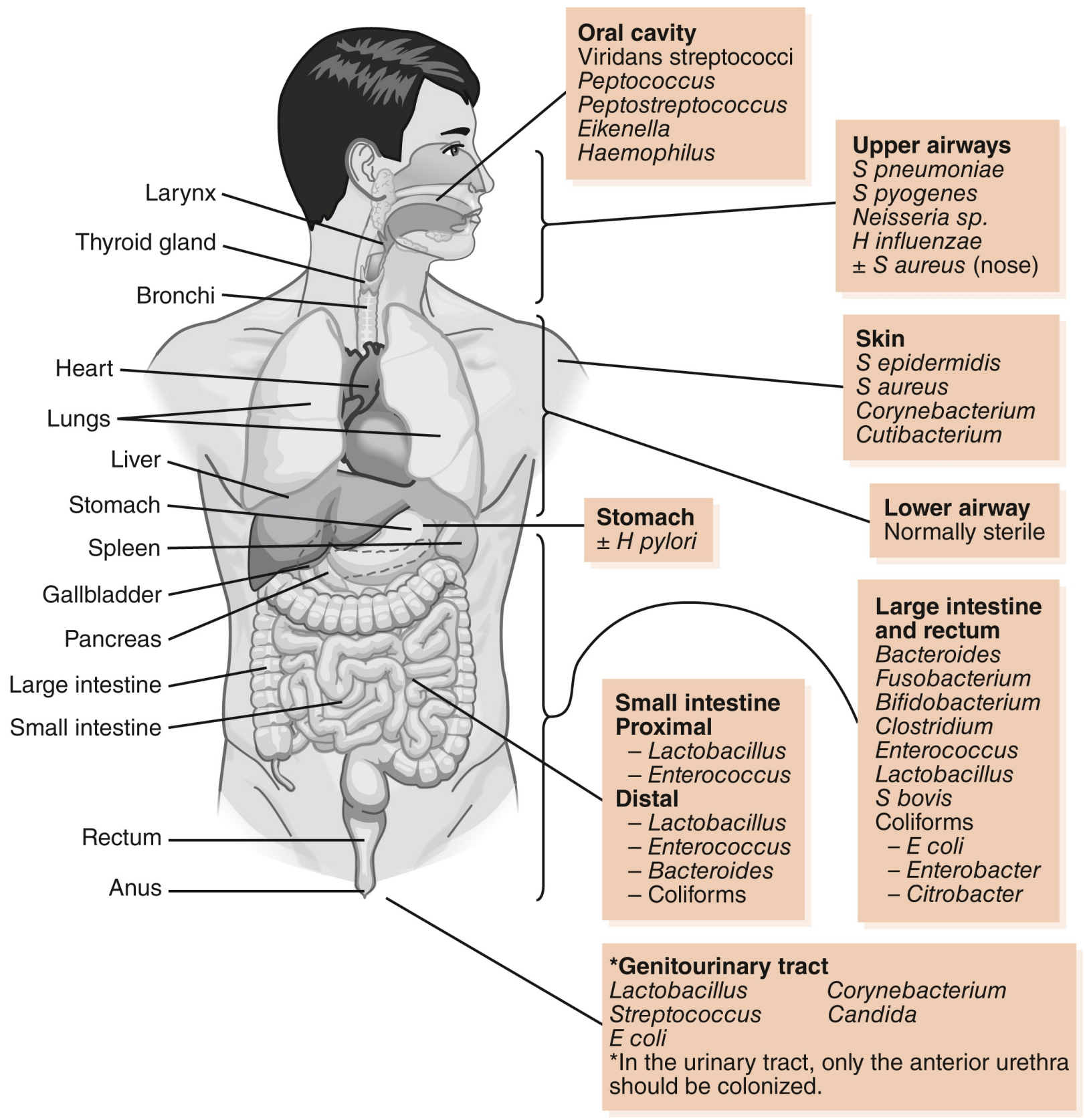
APPENDIX 1

SELECTED NORMAL HUMAN FLORA


Larynx
Thyroid gland
Bronchi
Heart
Lungs
Liver
Stomach
Spleen
Gallbladder
Pancreas
Large intestine
Small intestine
Rectum
Anus
Oral cavity
Viridans streptococci
Peptococcus
Peptostreptococcus
Eikenella
Haemophilus
Upper airways
S pneumoniae
S pyogenes
Neisseria sp.
H influenzae
± S aureus (nose)
Skin
S epidermidis
S aureus
Corynebacterium
Cutibacterium
Lower airway
Normally sterile
Stomach
± H pylori
Small intestine
Proximal
– Lactobacillus
– Enterococcus
Distal
– Lactobacillus
– Enterococcus
– Bacteroides
– Coliforms
Large intestine and rectum
Bacteroides
Fusobacterium
Bifidobacterium
Clostridium
Enterococcus
Lactobacillus
S bovis
Coliforms
– E coli
– Enterobacter
– Citrobacter
*Genitourinary tract
Lactobacillus
Streptococcus
E coli
Corynebacterium
Candida
*In the urinary tract, only the anterior urethra should be colonized.

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APPENDIX 2

SPECTRUM OF ACTIVITY

A Note on Spectrum of Activity

Spectrum of activity is usually thought of as "does this drug cover this pathogen?" It is important to realize that this is a substantial oversimplification. A more accurate statement would be, "What is the probability, in this patient, that the pathogen I am concerned about is susceptible to this antibiotic?" The key components are "probability" and "in this patient." Some antibiotics are *always* active against some organisms (e.g., penicillin and *Streptococcus pyogenes*), and a fair number of antibiotics are *never* active against some organisms at safe concentrations (e.g., vancomycin and *Escherichia coli*). But it is more common that there is some degree of variability in susceptibility across different isolates of the organism, and that there is variability in this variability! For example, **TABLE A-1** describes the susceptibility of *E coli* to ciprofloxacin at three hospitals—Major Medical Center, Trauma Hospital, and the Regional Children's Hospital—all located in the same city. (This example is based on actual data, but the names have been changed to protect the "innocent" institutions.)

TABLE A-1 Susceptibility of E coli to Ciprofloxacin at Three Hospitals

Antimicrobial	Organism	Year	Site	% Susceptible
Ciprofloxacin	*E coli*	1998	Major Medical Center: Adults	96.3
Ciprofloxacin	*E coli*	2008	Major Medical Center: Adults	58.0
Ciprofloxacin	*E coli*	2008	Trauma Hospital	85.0
Ciprofloxacin	*E coli*	2008	Regional Children's Hospital	94.0

Description

One key aspect of variability is time: You can see that in 1998, ciprofloxacin had excellent

activity against *E coli* isolated from inpatients at Major Medical Center. Over the next decade, its activity declined sharply. So it is important to keep "when" in perspective when reading the literature about spectrum of activity; sadly, the general trend is for susceptibility to decrease over time. Another aspect of variability is "where." Trauma Hospital is just on the other side of town from Major Medical Center, but among patients there, ciprofloxacin is much more active. There can be substantial geographic variability in susceptibility in different countries, states, regions, and even, as illustrated here, within a city. However, the variability in this case is most related to the last consideration, "who," as illustrated by the excellent activity of ciprofloxacin against *E coli* among patients at the Regional Children's Hospital. Regional Children's Hospital is located *within* the Major Medical Center (different floors of the same building), so it is not a matter of geography **per se**. Those patients are less likely to be exposed to fluoroquinolones and thus less likely to develop and spread resistant organisms to each other. So to best answer the question, "Does ciprofloxacin cover *E coli* in this city?", you want to know when the data were collected, where the patient acquired the infection, and who the patient is (in terms of risk factors for resistance).

With that caution, no one can hold all of the different percentage susceptibilities for different drug–pathogen combinations in their heads, so learning general patterns of susceptibility is the first step. **TABLE A-2** and **TABLE A-3** represent the *usual* (average across most areas and patient populations), *clinically useful* (not just good in the test tube) spectrum of activity for antibiotics and antifungals for *empiric* use. (If you already know what the organism is susceptible to, you don't need this chart.)

TABLE A-2 Clinically Useful Spectra of Activity for Empiric Antibiotic Selection for Most Commonly Used Antibacterials

	MSSA	MRSA	Strep	Enterococci	GNR	Pseudo	Anaerobes*	Atypicals
Penicillin G			++	+				
Ampicillin			++	++	+			
Amp/Sulb	++		++	++	+		++	
Pip/Tazo	++		++	++	++	++	++	
Cefazolin	++		++		+			
Cefuroxime	+		+		++			
Cefotetan	+		+		++		+	
Ceftriaxone	+		++		++			
Ceftazidime					++	++		
Cefepime	+		++		++	++		
Ceftaroline	++	++	++		++			
Cefiderocol					++	++		
Aztreonam					++	++		

Imipenem/ Meropenem	++		++	+	++	++	++	
Ertapenem	++		++		++		++	
Gent/Tobra	(syn†)		(syn†)	(syn†)	++	++		
Ciprofloxacin	+/–				++	+		++
Levofloxacin	+		++	+/–	++	+		++
Moxifloxacin	+		++	+/–	++		+/-	++
Doxycycline	+	+	+	+/–	+/-			++
Tigecycline	++	++	++	++	++		++	++
Clindamycin	++	+	+				+	
Vancomycin	++	++	++	++				
Azithromycin	+/–		+/-		+/-			++
Metronidazole							++	
Daptomycin	++	++	++	++				
Linezolid	++	++	++	++				
Nitrofurantoin				+	+			
Fosfomycin				+	++	+/-		
TMP/SMX	++	++	+/–		+			

Key: ++ = good activity; + = some activity; +/– = variable activity.
* Anaerobes here include GI anaerobes except *Clostridioides difficile*, for which the only antibiotics with useful clinical activity on this list are vancomycin and metronidazole.
† Aminoglycosides have useful synergistic activity versus gram-positive cocci only when paired with a cell-wall active agent (e.g., beta-lactams, vancomycin).
Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; Strep = streptococci; GNR = aerobic gram-negative rods (in general, and not including *Pseudomonas aeruginosa*); Pseudo = *Pseudomonas aeruginosa*; Imi/Mero/Dori=imipenem, meropenem, doripenem; Gent/Tobra=gentamicin, tobramycin; Amp/Sulb = ampicillin/sulbactam; Pip/Tazo = piperacillin/tazobactam; Quin/Dalf = quinupristin/dalfopristin; TMP/SMX = trimethoprim/sulfamethoxazole.

Description

TABLE A-3 Clinically Useful Spectra of Activity for Empiric Antifungal Selection

	Candida albicans, Candida parapsilosis, Candida tropicalis	*Candida glabrata*	*Candida krusei*	*Cryptococcus*	*Aspergillus*	*Mucorales*
Fluconazole	++	+/–		++		
Itraconazole	++	+/–	+/–	++	+	
Voriconazole	++	+	+	++	++	
Posaconazole/ isavuconazole	++	+	+	++	++	+
Amphotericin B*	++	+	++	++	++	++
Anidula/Caspo/Mica	++	++	++		+	

Key: *Active in vitro, but not indicated for treatment of Candida infections, ++ = good activity; + = some activity; +/– = variable activity.
Abbreviation: Anidula/Caspo/Mica = anidulafungin, caspofungin, micafungin.

Description

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APPENDIX 3

EMPIRIC REGIMENS FOR COMMON INFECTIONS

Infection	Common Pathogens	Patient/Infection Factors	Initial Empiric Therapy Options
Community-acquired pneumonia	*Streptococcus pneumoniae* *Haemophilus influenzae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Legionella pneumophila*	Outpatient, otherwise healthy, no recent antibiotic exposure	Doxycycline or azithromycin or clarithromycin or amoxicillin
		Outpatient, comorbidities and/or recent antibiotic exposure	Amoxicillin or amoxicillin/clavulanate or cefuroxime *-Plus-* azithromycin or clarithromycin *-Or-* levofloxacin or moxifloxacin or gemifloxacin

		Inpatient, non-ICU	Ceftriaxone or cefotaxime or ampicillin or ertapenem *-Plus-* azithromycin or clarithromycin or doxycycline *-Or-* levofloxacin or moxifloxacin
		Inpatient, ICU	Ceftriaxone or cefotaxime or ampicillin/sulbactam *-Plus-* azithromycin or levofloxacin or moxifloxacin
Hospital-acquired pneumonia	*Staphylococcus aureus* (MSSA) *Pseudomonas aeruginosa* Enterobacterales	Not at high risk of mortality; no factors increasing MRSA likelihood	
	As above plus: *Staphylococcus aureus* (MRSA)	Not at high risk or mortality, but with factors increasing likelihood of MRSA antibiotic exposure	Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam *-Plus-* vancomycin or linezolid
	As above	High risk of mortality or receipt of IV antibiotic within 90 days	Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam *-Plus-* Amikacin or tobramycin or gentamicin or levofloxacin or ciprofloxacin *-Plus-* vancomycin or linezolid

Ventilator-associated pneumonia	*Staphylococcus aureus* (MSSA or MRSA) *Pseudomonas aeruginosa* Enterobacterales	High rates of GNR resistance, MRSA (linezolid or vancomycin not needed if rates are low)	Linezolid or vancomycin *-Plus-* Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam *-Plus-* Amikacin or tobramycin or gentamicin or levofloxacin or ciprofloxacin or polymyxin B* or colistin* (*not preferred)
Otitis media	Viruses *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxaella catarrhalis*	Mild–moderate otalgia with temperature ≤39°C	Amoxicillin or cefuroxime or cefpodoxime or azithromycin
		Severe otalgia and/or temperature ≥39°C	Amoxicillin/clavulanate or ceftriaxone
Pharyngitis	Viruses *Streptococcus pyogenes*	Documented or high risk for *Streptococcus pyogenes*	Penicillin VK or cephalexin or azithromycin
Urinary tract infections	*Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Staphylococcus saphrophyticus* *Enterococcus* species	Uncomplicated community-acquired lower urinary tract infection in healthy women <50 years old	TMP/SMX or nitrofurantoin or fosfomycin or ciprofloxacin or levofloxacin (fluoroquinolones less preferred if alternatives can be used)
		Community-acquired complicated urinary tract infection or pyelonephritis	Ciprofloxacin or levofloxacin or ceftriaxone or ertapenem

	As above plus: *Enterobacter* species *Pseudomonas aeruginosa*	Nosocomial complicated urinary tract infection or pyelonephritis	Ceftazidime or piperacillin/tazobactam or cefepime or meropenem or imipenem
Skin/soft tissue infections	*Streptococcus pyogenes* *Staphylococcus aureus*	Low risk for MRSA (e.g., non-pustular)	Cefazolin or nafcillin or cephalexin or dicloxacillin
		High risk for MRSA (e.g., abscess, history)	Vancomycin or linezolid *-Or-* TMP/SMX *-Or-* cephalexin or dicloxacillin *-Or-* doxycycline
	As above plus: *Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Bacteroides fragilis* *Enterococcus* species *Pseudomonas aeruginosa*	Diabetic foot infection, moderate to severe	Ceftriaxone or ampicillin/sulbactam or piperacillin/tazobactam or ertapenem *-Or-* levofloxacin or ciprofloxacin *-Plus-* clindamycin All *with* or *without* vancomycin or linezolid
Intra-abdominal infections	*Escherichia coli* *Proteus* species *Klebsiella pneumoniae* *Bacteroides fragilis* *Enterococcus* species viridans *Streptococcus*	Community-acquired, mild–moderate severity	Ertapenem *-Or-* ceftriaxone or levofloxacin or ciprofloxacin *-Plus-* metronidazole
Community-acquired meningitis	*Streptococcus pneumoniae* *Neisseria meningitidis*	Otherwise healthy, 2–50 years of age	Ceftriaxone *-Plus-* vancomycin

	As above plus: *Listeria monocytogenes*	>50 years of age or immunocompromised	Ceftriaxone *-Plus-* vancomycin *-Plus-* ampicillin
Healthcare-associated infectious diarrhea	*Clostridioides difficile*	First episode	Fidaxomicin or vancomycin (oral)
		Recurrent episodes	Fidaxomicin or vancomycin (oral) tapered/pulsed dosing
		Recurrent episode within 6 months	Fidaxomicin or vancomycin (oral) *-Plus-* bezlotoxumab
Community-acquired infectious diarrhea	*Shigella* *Salmonella* *Escherichia coli* *Campylobacter* *Clostridioides difficile* (uncommon without antibiotic exposure)		Fluoroquinolone or TMP/SMX if antibiotic therapy is necessary

Description

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Prokaryotes are shown on the left under less like us. Viruses, bacteria, and archaea are under prokaryotes. Under viruses, herpesviruses are shown with H S V, V Z V, E B V, and C M V listed under herpesviruses. Gram positive, gram negative, and atypical bacteria are different kinds of bacteria. Mycoplasma and Chlamydia are listed under atypical bacteria. Eukaryotes and mammals are shown on the right under more like us. Fungi and parasites come under eukaryotes. Yeasts, dimorphic fungi, and molds are different types of fungi. Candida and Cryptococcus are under yeasts. Aspergillus and Zygomycetes are under molds. Coccidioides and Blastomyces are under dimorphic fungi. Protozoa and helminths are different types of parasites. Giardia and Plasmodium are under protozoa and Taenia and Ascaris are under helminths.

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The sizes of various organisms are indicated in the chart as follows: Under molecules: Egg albumin molecule, 10; and Hemoglobin molecule, 15. Under viruses: Tobacco mosaic, 15; foot and mouth, 21; yellow fever, 22; poliomyelitis, 27; T 2 bacteriophage, 65; Advenovirus, 75; influenza, 85; Rabies, 125; Herpes simplex, 130; and Vaccinia, 210. Under bacteria: Rickettsia, 250; and Streptococcus, 750. The size of red blood cell, under bacteria, viruses, and molecules, is indicated as 7,500.

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In gram positive cell wall, cell membrane is covered by peptidoglycan. In gram negative cell wall, cell membrane is covered by peptidoglycan, which in turn is covered by outer membrane. A cylindrical porin channel permeates through all three layers.

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Gram positive leads to Cocci and Bacilli. Cocci on the left leads to Anaerobic and Aerobic. Anaerobic leads to Peptococcus and Peptostreptococcus. Aerobic leads to Catalase positive, clusters, pairs and chains, and Catalase negative. Catalase positive leads to Coagulase positive and Coagulase negative. Coagulase positive leads to Staphylococcus aureus. Coagulase negative leads to Staphylococcus epidermidis and Staphylococcus saprophyticus. Catalase negative leads to alpha

hemolysis, beta hemolysis, and nonhemolytic. Alpha hemolysis leads to Streptococcus pneumoniae and Viridans streptococci. Beta hemolysis leads to Streptococcus pyogenes (Group A) and Streptococcus agalactiae (Group B). Nonhemolytic leads to Enterococcus faecium and Enterococcus faecalis. Bacilli on the right leads to Anaerobic and Aerobic. Anaerobic leads to Lactobacillus, Propionibacterium, Actinomyces, and Clostridium. One branch from Aerobic leads to Corynebacterium and Listeria and the other branch leads to Lactobacillus, Gardnerella, and Bacillus.

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Gram negative leads to Bacilli and Cocci. Bacilli on the left leads to Anaerobic and Aerobic. Anaerobic leads to Bacteroides, Prevotella, and Fusobacterium. Aerobic leads to rapid growth on standard agar and fastidious organisms. Rapid growth on standard agar leads to Glucose fermenters and Nonfermenters. Glucose fermenters lead to Vibrio and Aeromonas, and Enterobacteriaceae: Escherichia, Klebsiella, Serratia, Enterobacter, Citrobacter, Proteus, Salmonella, and Shigella. Nonfermenters lead to Pseudomonas, Acinetobacter, Stenotrophomonas, and Burkholderia. Fastidious organisms lead to Haemophilus, Campylobacter, Helicobacter, Bartonella, and H A C E K organisms. Cocci on the right leads to Neisseria and Moraxella. Acinetobacter, Moraxella, and Haemophilus may appear as coccobacilli. H A C E K organisms stand for Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella.

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The top end of a triangle represents Pathogen, left end represents Drug, and the right end represents Patient. Arrow from pathogen toward patient represents infection and the arrow from patient toward pathogen represents immune response. Arrow from drug toward pathogen represents pharmacodynamics and the arrow from pathogen toward drug represents resistance mechanisms. Arrow from drug toward patient represents pharmacodynamics (toxicity) and the arrow from patient toward drug represents pharmacokinetics.

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The flow diagram flows downward as follows: Suspect infection, culture suspected

sites, gram stain, identification, and susceptibilities. Begin empiric therapy for likely pathogens after culturing suspected sites and before gram stain. After susceptibilities, change to definitive therapy for patient specific pathogens.

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The x axis represents time and the y axis represents antibiotic concentration. The time of administration to the time of peak concentration is indicated as absorption where the antibiotic concentration increases drastically. Absorption phase is followed by distribution phase where the concentration decreases at a faster pace. Distribution phase is followed by metabolism and excretion where the concentration decreases at a slower pace. The excretion phase ends at the lowest level of concentration indicated as trough concentration. The region covered by the curve is indicated as area under the curve.

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Drug, bioavailability, typical intravenous dose, and typical oral dose are the four column heads of the table. Under the panel, Drugs with High Bioavailability and Similar Intravenous, Oral Doses, the following row entries are shown: Metronidazole, 95 to 100 percent, 500 milligrams fourth q 8 h, and 500 milligrams p o q 8 h. Levofloxacin, 95 to 100 percent, 500 to 750 milligrams fourth q 24 h, and 500 to 750 milligrams p o daily. Linezolid, 95 to 100 percent, 600 milligrams fourth q 8 h, and 600 milligrams p o q 12 h. Fluconazole, 95 to 100 percent, 200 to 400 milligrams fourth daily, and 200 to 400 milligrams p o daily. Doxycycline, 95 to 100 percent, 100 milligrams fourth q 12 h, and 100 milligrams p o q 12 h. Ciprofloxacin, approximately 80 percent, 400 milligrams fourth q 12 h, and 500 milligrams p o q 12 h. Under the panel, Drugs with High Bioavailability but Different Intravenous, Oral Doses, the following row entries are shown. Aminopenicillins, approximately 90 percent, Ampicillin: 1 to 2 grams fourth q 4 to 6 h, and Amoxicillin: 500 milligrams to 1 gram p o t i d. First-generation cephalosporins, approximately 90 percent, Cefazolin: 1 to 2 grams fourth q 8 h, and Cephalexin: 500 milligrams p o q i d. Under the panel, Drugs with Low Bioavailability and Different Intravenous, Oral Doses, the following row entries are shown. Cefuroxime, approximately 40 percent, 750 milligrams fourth q 8 h, and 500 milligrams p o b i d. Acyclovir, approximately 25 percent, 5 milligrams per kilogram fourth q 8 h, and 400 milligrams p o t i d.

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Under the column head, Absorption Improved with Food, the following antibiotics are listed: Posaconazole suspension, Itraconazole capsules, Atazanavir, Darunavir, and Rilpivirine. Under the head, Absorption Impaired by Food, the following antibiotics are listed: Voriconazole, Itraconazole solution, Omadacycline, Rifampin, Isoniazid, and Pyrazinamide. Under the head, Absorption Impaired by Drugs That Increase Gastric p H, the following antibiotics are listed: Itraconazole, Posaconazole suspension, Atazanavir, and Rilpivirine. Under the head, Absorption Impaired by Minerals, the following antibiotics are listed: Fluoroquinolones, Tetracyclines, Bictegravir, and Dolutegravir.

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On the top, concentration of antibiotic in milligrams per liter is indicated as 32, 16, 8, and 4 in four test tubes. The four test tubes indicate no visible organism growth in broth. Bacterial colonies on agar plates are shown for each of the test tubes. No bacterial colonies are found in agar plates with antibiotic concentration of 32 and 16 milligrams per liter. Less bacterial colonies are found for a concentration of 8 milligrams per liter and more bacterial colonies are found for a concentration of 4 milligrams per liter. Test tube with antibiotic concentration of 4 milligrams per liter is indicated as M I C equals 4. Agar plate with concentration of 16 milligrams per liter is indicated as M B C equals 16. At the bottom, four test tubes show visible organism growth in broth with 2, 1, 0.5, and 0.25 indicated for the test tubes from left to right.

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Organism Antibiotics; Susceptible (Breakpoint); Susceptible, Dose-Dependent; Intermediate; and Resistant are the five column heads of the table. Under the panel, Escherichia Coli, the following row entries are shown: Row 1: Ampicillin, less than or equal to 8 milligrams per liter, dash, 16 milligrams per liter, and greater than or equal to 32 milligrams per liter. Row 2: Cefepime, less than or equal to 2 milligrams per liter, 4 to 8 milligrams per liter, dash, and greater than or equal to 16 milligrams per liter. Row 3: Levofloxacin, less than or equal to 0.5 milligrams per liter, dash, 1 milligram per liter, and greater than or equal to 2 milligrams per liter. Row 4: Trimethoprim or sulfamethoxazole, less than or equal to 2 over 38 milligrams per

liter, dash, dash, and greater than or equal to 4 over 76 milligrams per liter. Under the panel, Streptococcus pneumonia, the following row entries are shown: Row 5: Ampicillin, dash, dash, dash, and dash. Row 6: Cefepime (meningitis) (Nonmeningeal), less than or equal to 0.5 milligrams per liter and less than or equal to 1 milligrams per liter, dash and dash, 1 milligram per liter and 2 milligrams per liter, and greater than or equal to 2 milligrams per liter and greater than or equal to 4 milligrams per liter. Row 7: Levofloxacin, less than or equal to 2 milligrams per liter, dash, 4 milligrams per liter, and greater than or equal to 8 milligrams per liter. Row 8: Trimethoprim or sulfamethoxazole, less than or equal to 0.5 over 9.5 milligrams per liter, dash, 1 to 2 over 19 to 38 milligrams per liter, and greater than or equal to 4 over 76 milligrams per liter.

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The x axis of the graph represents time and the y axis represents concentration. The curve increases drastically in concentration in less time and reaches its peak. Then the concentration level decreases gradually as time increases. A dotted horizontal line above the x axis represents M I C. The area under the curve is shaded and indicated as A U C. The vertical distance from the peak to M I C is indicated as Peak: M I C. The horizontal distance of M I C within the curve is indicated as time greater than M I C.

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Decreased penetration, enzymatic modification, target site changes, and active efflux are the four mechanisms of antibiotic resistance. In decreased penetration, A b x cells representing antibiotic do not penetrate into the cell wall. In enzymatic modification, an enzyme carrying A b x loses A b x after reaching the bacterial cell. In target site changes, A b x bonded to a site of action is lost in the site. In active efflux, efflux pumps out A b x.

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The left pane represents better against staphylococci and the right pane represents Better against G N Rs. Natural penicillins lead to Antistaphylococcal penicillins in the left pane, which in turn leads to Beta-lactam or beta-lactamase inhibitor combinations, which exists on both left and the right panes. Natural penicillins also

lead to Aminopenicillins in the right pane, which in turn leads to Antipseudomonal penicillins, which in turn leads to Beta-lactam or beta-lactamase inhibitor combinations.

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A frame at the center reads as follows from top to bottom: Cefazolin first, Cefuroxime second, Ceftriaxone third, Cefepime fourth, and Ceftaroline Anti M R S A. To the left of the frame, gram positive activity represents a diagram, and to the right, gram negative activity represents a diagram. The diagram on the left is in the form of an inverted triangle on the tip of another triangle at the bottom. The inverted triangle converges from the first till the fourth of the center frame. The diagram on the right extends from the bottom till the fourth of the center frame. From the fourth till the first, it contracts and converges to a tip point.

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Indication, Ciprofloxacin, Levofloxacin, Moxifloxacin, and Delafloxacin are the five column heads of the table. The row entries are as follows: C A P, sinusitis, A E C B; minus; plus; plus; and plus. U T I; plus; plus; minus; and question mark. Intra-abdominal infection; plus; plus; plus; and question mark. Systemic gram-negative infections; plus; plus; plus; question mark. Skin or soft tissue infection; minus; plus; plus; and plus. Pseudomonas infections; plus; plus; minus; and question mark. Treatment or prophylaxis in bioterrorism scenarios (active versus anthrax, plague, tularemia); plus; plus; question mark; and minus. A note at the bottom indicates the following: plus equals approved or studied or makes sense for this indication. Question mark equals should work, no clinical data. Minus equals suboptimal.

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The outermost to the inner layers are shown as follows: extractable phospholipids, mycolic acids, arabinogalactan, peptidoglycan, and cytoplasmic membrane. Pores extend from extractable phospholipids to peptidoglycan.

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Drug, Fluconazole tablets, Voriconazole tablets, Itraconazole, Posaconazole, and Isavuconazole are the column heads of the table. Itraconazole column is further

divided into three subcolumns: Regular capsules, S U B A itraconazole capsules, and Solution. Posaconazole column is further divided into two subcolumns: Solution and Tablets. The row entries read as follows: Row 1: Drug, Food. Fluconazole tablets, Administer with or without food. Voriconazole tablets, Administer on empty stomach (1 hour separate from food). Itraconazole regular capsules, Administer with food. S U B A itraconazole capsules, Administer with food. Itraconazole solution, Administer on empty stomach (1 hour separate from food). Posaconazole solution, Administer with high-fat meal. Posaconazole tablets, Administer with food. Isavuconazole, Give with or without food. Row 2: Drug, Antacids. A footnote for antacids reads as follows: Histamine-2 receptor antagonists, cation-based antacids (calcium, magnesium, aluminum). Fluconazole tablets, No effect. Voriconazole tablets, No effect. Itraconazole regular capsules, Avoid. S U B A itraconazole capsules, Unclear, consider avoiding. Itraconazole solution, No effect. Posaconazole solution, Avoid. Posaconazole tablets, No effect. Isavuconazole, No effect. Row 3: Drug, Proton-pump inhibitors. Fluconazole tablets, No effect. Voriconazole tablets, Increases voriconazole levels. Itraconazole regular capsules, Decreases itraconazole levels. S U B A itraconazole capsules, Increases itraconazole levels. Itraconazole solution, Unclear. Posaconazole solution, Decreases posaconazole levels. Posaconazole tablets, No effect. Isavuconazole, No effect.

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Group, subgroup, examples, and antiparasitics are the four column heads of the table. A footnote for antiparasitics reads as follows: Agents in bold are discussed in Part 6; agents in normal type are covered in other chapters; agents in italics are not discussed in this book. The row entries are as follows: Row 1: Group, Protozoa. Subgroup, Extraintestinal. Examples, Plasmodium (malaria) and Toxoplasma. Antiparasitics, Quinolines, in bold; Doxycycline, in normal; Clindamycin, in normal; Atovaquone-proguanil, in bold; Arteminsins, in bold; Pyrimethamine or Sulfadiazine, in normal; and T M P or S M X, in normal. Row 2: Group, Protozoa. Subgroup, Extraintestinal. Examples, Trypansoma. Antiparasitics, Pentamidine, in bold. Row 3: Group, Protozoa. Subgroup, Intestinal. Examples, Entamoeba, Giardia, and Cryptosporidium. Antiparasitics, Metronidazole, in normal; Tinidazole, in normal; Paromomycin, in italics. Row 4: Group, Helminths. Subgroup, Nematodes. Examples, Ascaris and Strongyloides. Antiparasitics, Albendazole, in bold, and

Ivermectin, in bold. Row 5: Group, Helminths. Subgroup, Trematodes. Examples, Schistosoma. Antiparasitics, Praziquantel, in italics. Row 6: Group, Helminths. Subgroup, Cestodes. Examples, Echinococcus and Taenia. Antiparasitics, Albendazole, in bold, and Praziquantel, in italics. Row 7: Group, Other organisms. Subgroup, Fungus. Examples, Pneumocystis. Antiparasitics, T M P or S M X, in normal; Clindamycin, in normal, or Primaquine, in bold; Atovaquone, in bold; and Pentamidine, in bold. Row 8: Group, Other organisms. Subgroup, Ectoparasites. Examples, Scabies. Antiparasitics, Ivermectin, in bold.

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Antimicrobial, organism, year, site, and percentage susceptible are the five column heads of the table. The row entries are as follows: Row 1: Ciprofloxacin, E coli, 1998, Major Medical Center: Adults, and 96.3. Row 2: Ciprofloxacin, E coli, 2008, Major Medical Center: Adults, and 58.0. Row 3: Ciprofloxacin, E coli, 2008, Trauma Hospital, and 85.0. Row 4: Ciprofloxacin, E coli, 2008, Regional Children’s Hospital, and 94.0.

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M S S A, M R S A, Strep, Enterococci, G N R, Pseudo, Anaerobes, and Atypicals are the eight column heads of the table. Anaerobes here include G I anaerobes except Clostridioides difficile, for which the only antibiotics with useful clinical activity on this list are vancomycin and metronidazole. Double plus, single plus, or plus or minus is indicated under selected columns for each of the row heads and the other columns are blank. A key at the bottom indicates that double plus equals good activity, single plus equals some activity, and plus or minus equals variable activity. The row heads and entries of the table are as follows: Penicillin G: Strep, double plus. Enterococci, single plus. Ampicillin: Strep, double plus. Enterococci, double plus. G N R, single plus. Amp or Sulb: M S S A, double plus. Strep, double plus. Enterococci, double plus. G N R, single plus. Anaerobes, double plus. Pip or Tazo: M S S A, double plus. Strep, double plus. Enterococci, double plus. G N R, double plus. Pseudo, double plus. Anaerobes, double plus. Cefazolin: M S S A, double plus. Strep, double plus. G N R, single plus. Cefuroxime: M S S A, single plus. Strep, single plus. G N R, double plus. Cefotetan: M S S A, single plus. Strep, single plus. G N R, double plus. Anaerobes, single plus. Ceftriaxone: M S S A, single plus. Strep, double plus. G N R, double plus. Ceftazidime: G N R, double plus. Pseudo,

double plus. Cefepime: M S S A, single plus. Strep, double plus. G N R, double plus. Pseudo, double plus. Ceftaroline: M S S A, double plus. M R S A, double plus. Strep, double plus. G N R, double plus. Cefiderocol: G N R, double plus. Pseudo, double plus. Aztreonam: G N R, double plus. Pseudo, double plus. Imipenem or Meropenem: M S S A, double plus. Strep, double plus. Enterococci, single plus. G N R, double plus. Pseudo, double plus. Anaerobes, double plus. Ertapenem: M S S A, double plus. Strep, double plus. G N R, double plus. Anaerobes, double plus. Gent or Tobra: M S S A, (syn). Strep, (syn). Enterococci, (syn). G N R, double plus. Pseudo, double plus. Dagger symbol for syn reads as follows in the footnote: Aminoglycosides have useful synergistic activity versus gram-positive cocci only when paired with a cell-wall active agent (for example, beta-lactams, vancomycin). Ciprofloxacin: M S S A, plus or minus. G N R, double plus. Pseudo, single plus. Atypicals, double plus. Levofloxacin: M S S A, single plus. Strep, double plus. Enterococci, plus or minus. G N R, double plus. Pseudo, single plus. Atypicals, double plus. Moxifloxacin: M S S A, single plus. Strep, double plus. Enterococci, plus or minus. G N R, double plus. Anaerobes, single plus. Atypicals, double plus. Doxycycline: M S S A, single plus. M R S A, single plus. Strep, single plus. Enterococci, plus or minus. G N R, plus or minus. Atypicals, double plus. Tigecycline: M S S A, double plus. M R S A, double plus. Strep, double plus. Enterococci, double plus. G N R, double plus. Anaerobes, double plus. Atypicals, double plus. Clindamycin: M S S A, double plus. M R S A, single plus. Strep, single plus. Anaerobes, single plus. Vancomycin: M S S A, double plus. M R S A, double plus. Strep, double plus. Enterococci, double plus. Azithromycin: M S S A, plus or minus. Strep, plus or minus. G N R, plus or minus. Atypicals, double plus. Metronidazole: Anaerobes, double plus. Daptomycin: M S S A, double plus. M R S A, double plus. Strep, double plus. Enterococci, double plus. Linezolid: M S S A, double plus. M R S A, double plus. Strep, double plus. Enterococci, double plus. Nitrofurantoin: Enterococci, single plus. G N R, single plus. Fosfomycin: Enterococci, single plus. G N R, double plus. Pseudo, plus or minus. T M P or S M X: M S S A, double plus. M R S A, single plus. Strep, plus or minus. G N R, single plus. Abbreviations: M S S A equals methicillin-susceptible Staphylococcus aureus; M R S A equals methicillin-resistant Staphylococcus aureus; Strep equals streptococci; G N R equals aerobic gram-negative rods (in general, and not including Pseudomonas aeruginosa); Pseudo equals Pseudomonas aeruginosa; Imi or Mero or Dori equal imipenem, meropenem, doripenem; Gent or Tobra equals gentamicin, tobramycin; Amp or Sulb equals ampicillin or sulbactam; Pip or Tazo

equals piperacillin or tazobactam; Quin or Dalf equals quinupristin or dalfopristin; T M P or S M X equals trimethoprim or sulfamethoxazole.

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Candida albicans, Candida parapsilosis, Candida tropicalis; Candida glabrata; Candida krusei; Cryptococcus; Aspergillus; and Mucorales are the column heads of the table. The row heads and entries of the table are as follows: Row 1: Fluconazole. Column 1, double plus. Candida glabrata, plus or minus. Cryptococcus, double plus. Row 2: Itraconazole. Column 1, double plus. Candida glabrata, plus or minus. Candida krusei: plus or minus. Cryptococcus, double plus. Aspergillus, single plus. Row 3: Voriconazole. Column 1, double plus. Candida glabrata, single plus. Candida krusei, single plus. Cryptococcus, double plus. Aspergillus, double plus. Row 4: Posaconazole or isavuconazole. Column 1, double plus. Candida glabrata, single plus. Candida krusei, single plus. Cryptococcus, double plus. Aspergillus, double plus. Mucorales, single plus. Row 5: Amphotericin B. Column 1, double plus. Candida glabrata, single plus. Candida krusei, double plus. Cryptococcus, double plus. Aspergillus, double plus. Mucorales, double plus. Row 6: Anidula or Caspo or Mica. Column 1, double plus. Candida glabrata, double plus. Candida krusei, double plus. Aspergillus, single plus. A note at the bottom reads as follows: Key: double plus equals good activity; plus equals some activity; plus or minus equals variable activity. Abbreviation: Anidula or Caspo or Mica equals anidulafungin, caspofungin, micafungin.

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Infection, common pathogens, patient and infection factors, and initial empiric therapy options are the four column heads of the table. The row entries are as follows: Infection: Community-acquired pneumonia. Common pathogens: Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila. Patient and infection factors: Outpatient, otherwise healthy, no recent antibiotic exposure. Initial empiric therapy options: Doxycycline or azithromycin or clarithromycin or amoxicillin. Patient and infection factors: Outpatient, comorbidities and or recent antibiotic exposure. Initial empiric therapy options: Amoxicillin or amoxicillin or clavulanate or cefuroxime Plus azithromycin or clarithromycin Or levofloxacin or moxifloxacin or gemifloxacin. Patient and infection factors: Inpatient, non I C U. Initial empiric therapy options:

Ceftriaxone or cefotaxime or ampicillin or ertapenem Plus azithromycin or clarithromycin or doxycycline Or levofloxacin or moxifloxacin. Patient and infection factors: Inpatient, I C U. Initial empiric therapy options: Ceftriaxone or cefotaxime or ampicillin or sulbactam Plus azithromycin or levofloxacin or moxifloxacin. Infection: Hospital-acquired pneumonia. Common pathogens: Staphylococcus aureus (M S S A), Pseudomonas aeruginosa, and Enterobacterales. Patient and infection factors: Not at high risk of mortality; no factors increasing M R S A likelihood. Common pathogens: As above plus: Staphylococcus aureus (M R S A). Patient and infection factors: Not at high risk or mortality, but with factors increasing likelihood of M R S A antibiotic exposure. Initial empiric therapy options: Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam Plus vancomycin or linezolid. Common pathogens: As above. Patient and infection factors: High risk of mortality or receipt of fourth antibiotic within 90 days. Initial empiric therapy options: Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam Plus Amikacin or tobramycin or gentamicin or levofloxacin or ciprofloxacin Plus vancomycin or linezolid. Infection: Ventilator-associated pneumonia. Common pathogens: Staphylococcus aureus (M S S A or M R S A), Pseudomonas aeruginosa, and Enterobacterales. Patient and infection factors: High rates of G N R resistance, M R S A (linezolid or vancomycin not needed if rates are low). Initial empiric therapy options: Linezolid or vancomycin Plus Piperacillin-tazobactam or cefepime or levofloxacin or imipenem or meropenem or aztreonam Plus Amikacin or tobramycin or gentamicin or levofloxacin or ciprofloxacin or polymyxin B asterisk or colistin asterisk (asterisk, not preferred). Infection: Otitis media. Common pathogens: Viruses, Streptococcus pneumoniae, Haemophilus influenza, and Moraxaella catarrhalis. Patient and infection factors: Mild and moderate otalgia with temperature less than or equal to 39 degree Celsius. Initial empiric therapy options: Amoxicillin or cefuroxime or cefpodoxime or azithromycin. Patient and infection factors: Severe otalgia and or temperature greater than or equal to 39 degree Celsius. Initial empiric therapy options: Amoxicillin and clavulanate or ceftriaxone. Infection: Pharyngitis. Common pathogens: Viruses Streptococcus pyogenes. Patient and infection factors: Documented or high risk for Streptococcus pyogenes. Initial empiric therapy options: Penicillin V K or cephalexin or azithromycin. Infection: Urinary tract infections. Common pathogens: Escherichia coli, Proteus species, Klebsiella pneumonia, Staphylococcus saphrophyticus, and Enterococcus species. Patient and infection factors: Uncomplicated community-acquired lower urinary tract

infection in healthy women less than 50 years old. Initial empiric therapy options: T M P or S M X or nitrofurantoin or fosfomycin or ciprofloxacin or levofloxacin (fluoroquinolones less preferred if alternatives can be used). Patient and infection factors: Community-acquired complicated urinary tract infection or pyelonephritis. Initial empiric therapy options: Ciprofloxacin or levofloxacin or ceftriaxone or ertapenem. Common pathogens: As above plus: Enterobacter species, Pseudomonas aeruginosa. Patient and infection factors: Nosocomial complicated urinary tract infection or pyelonephritis. Initial empiric therapy options: Ceftazidime or piperacillin and tazobactam or cefepime or meropenem or imipenem. Infection: Skin or soft tissue infections. Common pathogens: Streptococcus pyogenes, Staphylococcus aureus. Patient and infection factors: Low risk for M R S A (for example, non-pustular). Initial empiric therapy options: Cefazolin or nafcillin or cephalexin or dicloxacillin. Patient and infection factors: High risk for M R S A (for example, abscess, history). Initial empiric therapy options: Vancomycin or linezolid Or T M P or S M X Or Cephalexin or dicloxacillin Or doxycycline. Common pathogens: As above plus: Escherichia coli, Proteus species, Klebsiella pneumoniae, Bacteroides fragilis, Enterococcus species, and Pseudomonas aeruginosa. Patient and infection factors: Diabetic foot infection, moderate to severe. Initial empiric therapy options: Ceftriaxone or ampicillin or sulbactam or piperacillin or tazobactam or ertapenem Or levofloxacin or ciprofloxacin Plus clindamycin, All with or without vancomycin or linezolid. Infection: Intra-abdominal infections. Common pathogens: Escherichia coli, Proteus species, Klebsiella pneumoniae, Bacteroides fragilis, Enterococcus species, and viridans Streptococcus. Patient and infection factors: Community-acquired, mild and moderate severity. Initial empiric therapy options: Ertapenem Or ceftriaxone or levofloxacin or ciprofloxacin Plus metronidazole. Infection: Community-acquired meningitis. Common pathogens: Streptococcus pneumoniae and Neisseria meningitidis. Patient and infection factors: Otherwise healthy, 2 to 50 years of age. Initial empiric therapy options: Ceftriaxone Plus vancomycin. Common pathogens: As above plus: Listeria monocytogenes. Patient and infection factors: greater than 50 years of age or immunocompromised. Initial empiric therapy options: Ceftriaxone Plus vancomycin Plus ampicillin. Infection: Healthcare-associated infectious diarrhea. Common pathogens: Clostridioides difficile. Patient and infection factors: First episode. Initial empiric therapy options: Fidaxomicin or vancomycin (oral). Patient and infection factors: Recurrent episodes. Initial empiric therapy options: Fidaxomicin or vancomycin (oral) tapered or pulsed dosing. Patient

and infection factors: Recurrent episode within 6 months. Initial empiric therapy options: Fidaxomicin or vancomycin (oral) Plus bezlotoxumab. Infection: Community-acquired infectious diarrhea. Common pathogens: Shigella, Salmonella, Escherichia coli, Campylobacter, Clostridioides difficile (uncommon without antibiotic exposure). Initial empiric therapy options: Fluoroquinolone or T M P or S M X if antibiotic therapy is necessary.

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